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The neuropsychology of schizophrenia

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Abstract: A model is proposed for integrating the neural and cognitive aspects of the positive symptoms of acute schizophrenia, using evidence from postmortem neuropathology and neurochemistry, clinical and preclinical studies of dopaminergic neurotransmission, anatomical connections between the limbic system and basal ganglia, attentional and other cognitive abnormalities underlying the positive symptoms of schizophrenia, specific animal models of some of these abnormalities, and previous attempts to model the cognitive functions of the septohippocampal system and the motor functions of the basal ganglia. Anatomically, the model emphasises the projections from the septohippocampal system, via the subiculum, and the amygdala to nucleus accumbens, and their interaction with the ascending dopaminergic projection to the accumbens. Psychologically, the model emphasises a failure in acute schizophrenia to integrate stored memories of past regularities of perceptual input with ongoing motor programs in the control of current perception. A number of recent experiments that offer support for the model are briefly described, including anatomical studies of limbic-striatal connections, studies in the rat of the effects of damage to these connections, and of the effects of amphetamine and neuroleptics, on the partial reinforcement extinction effect, latent inhibition and the Kamin blocking effect; and studies of the latter two phenomena in acute and chronic schizophrenics.

Keywords: attentional deficit; basal ganglia; dopamine; limbic system; memory; neuroleptics; perception; schizophrenia; septohippocampal system

The neuropsychology of schizophrenia

In recent years there has been a notable increase in attempts to construct models of the neural dysfunction that underlies schizophrenia, considered either as a single diagnostic entity or after separation into subtypes or particular symptom clusters within this entity (e.g., Schmajuk 1987; Swerdlow & Koob 1987; Weinberger 1987). At the same time, other workers have tried to provide a fresh interpretation of schizophrenic symptomatology in terms of an underlying defect in specific aspects of cognitive functioning (e.g., Frith 1987; Hemsley 1987). There have even been a few fledgling attempts to grapple with the much more daunting task of constructing a model of schizophrenic dysfunction to encompass, and above all to integrate, both its neural and its cognitive aspects (Frith & Done 1988; Joseph et al. 1979; McKenna 1987; Swerdlow & Koob 1987a). It is our intention to offer here a tentative model of the latter kind.

The model aims to bring together: (1) the postmortem evidence of neuronal loss and cytopathology in limbic regions of the temporal lobe in schizophrenic brains (Beckmann et al. 1987; Bogerts et al. 1985; Brown et al. 1986; Jeste & Lohr 1989; but see Christison et al. 1989); (2) the evidence of specific neurotransmitter loss in these same regions (Roberts et al. 1983); (3) neuropharmacological evidence from both clinical and animal studies suggesting dopaminergic hyperactivity in at least the acute phase of a schizophrenic illness (Swerdlow & Koob 1987a); (4) recent advances in neuroanatomical knowledge of the connections between the limbic system and the basal ganglia (Kelley & Domesick 1982; Nauta & Domesick 1984; Totterdell & Smith 1986; 1989); (5) previous suggestions of specific attentional and other cognitive deficits in schizophrenia (Frith 1987; Hemsley 1987a); (6) specific animal models of some of these deficits (Solomon et al. 1981; Weiner et al. 1981; 1984; 1988; Weiner, Izraeli-Telerant & Feldon 1987f); (7) previous attempts to model some of the cognitive functions of the limbic system and basal ganglia in relation to the neuropsychology of anxiety (Gray 1982a; 1982b) and motor function (Groves 1983; Swerdlow & Koob 1987a); and, finally, (8) some of the specific symptoms of schizophrenia, especially the "positive" symptoms most characteristic of the acute stage of the illness.

Given the current state of knowledge in many of the relevant areas, much of the model is highly speculative. It is readily open to experimental testing at a number of points, however, not only with clinical material but also in experiments with animals. Until recently, animal models of schizophrenia seemed implausible, because clinical descriptions emphasised abnormalities in the sphere of

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language, such as verbal hallucinations or thought disorder. More recent models (e.g., those of Frith [1987] and Hemsley [1987a], both described below) have started to treat schizophrenic verbal abnormalities as stemming from a more basic deficit in cognitive capacities not necessarily limited to the language sphere (Schwartz 1982), however. The development of these models (themselves influenced at critical points by concepts derived from animal experiments) suggests that research with animals is now able to contribute to our understanding of not only the neurochemistry but also the neuropsychology of schizophrenia. Research of this kind from our own laboratories is described below.

1. The psychology of schizophrenia

We are seeking to explain the basic psychological dysfunction that characterises schizophrenia. This way of formulating the problem supposes that there indeed exists a basic psychological dysfunction in schizophrenia; or, at least, only a limited number of such dysfunctions. Here we shall consider two hypotheses as to the nature of the dysfunction: Hemsley's (1987a) proposal that "it is a weakening of the influences of stored memories of regularities of previous input on current perception," which is basic to the schizophrenic condition; and Frith's (1987) hypothesis that "willed intentions are not monitored correctly" in schizophrenia. Both these hypotheses have been shown to be able in principle to account for a wide variety of the clinical features of schizophrenia, though each is intended to apply principally to Type I (acute) rather than Type II (chronic) schizophrenic patients (in other words, to positive rather than negative schizophrenic symptoms, Crow 1989b). In the present context, this limitation is an advantage, because our main aim is to describe how an excess of dopaminergic activity can produce the symptomatic picture of acute schizophrenia. We, too, shall accordingly limit the discussion to positive symptoms, concentrating upon these two hypotheses not only because of their success in accounting for a variety of clinical and experimental observations with schizophrenic patients (see the discussions in Frith 1987; and Hemsley 1982; 1987), but also because each is readily compatible with the neural machinery adumbrated below.

The primary positive symptoms of acute schizophrenia for which an account must be sought (Frith 1979; 1987; Hemsley 1982; 1987a) include the occurrence of hallucinations (most commonly auditory and frequently verbal in content), delusions and thought disorder (e.g., such phenomena as derailment and neologisms). It has proved difficult, however, to specify "the psychological dysfunction (which is) the elusive core of the schizophrenia syndrome" (Shepherd 1987, p. 37). Studies of selective attention, which may be viewed as the major control process in the passage of information through the system, have been influential. Some clinical phenomena justify this emphasis. Thus Matussek (1952, p. 92) wrote of a patient who was aware of:

> a lack of continuity of his perceptions in both space and over time. He saw the environment only in fragments. There was no appreciation of the whole. He saw only details against a meaningless background.

Another patient reported:

> I was surrounded by a multitude of meaningless details.

There are nevertheless problems in inferring the precise nature of the attentional dysfunction, particularly when the experimental tasks yield cognitive deficits for which there are frequently plausible alternative explanations (cf, Knight 1984).

The accounts offered for these primary positive symptoms by Hemsley and Frith are not mutually exclusive; indeed, we shall show below how they can be integrated into a single neuropsychology. Hemsley's account originally focused on Broadbent's (1977) concept of "pigeonholing," the kind of attention that "selects some of the possible interpretations that a man may hold about the world and eliminates others as candidates for use in the particular situation." [See also Hoffman: "Verbal Hallucinations and Language Production Processes in Schizophrenia" *BBS* 9(3) 1986.] Pigeon-holing works by (1) integrating information from the present context and past experience of similar contexts and (2) biasing both the interpretation of current sensory input and the preparation of responses to that input in relation to the expected probabilities of events as derived from that integration. The many different theoretical models for schizophrenics' disturbances of perception and cognition often differ radically in their assumptions about the nature of normal information processing. Thus Nuechterlein and Dawson (1984) emphasise a reduction in available processing capacity in schizophrenia. Among the reasons are that "more processing capacity is devoted to task-irrelevant stimuli" and that "conscious capacity demanding processing is required to complete cognitive operations that are usually completed automatically in parallel processing" (op. cit., p. 193). Although it is clearly hazardous to interpret studies in a framework different from the one in which they were designed, we may consider seven current views as to the nature of schizophrenic cognitive impairment (Table 1, from Hemsley 1987a).

Several models of normal cognition suggest that awareness of redundant information is inhibited to reduce information processing demands on a limited capacity system. The change from controlled to automatic processing on a task may be seen as including a gradual inhibition of awareness of redundant information (Schneider & Schiffrin 1977). A related position has been adopted by Posner and his colleagues (e.g., Posner 1982). They distinguish automatic processes from conscious attention, the former not giving rise to awareness, the latter involving awareness and closely associated with a "general inhibitory process" (op. cit., p. 173). Cognitive abnormalities in schizophrenia might then be seen as related to a weakening of inhibitory processes crucial to conscious attention. Such a disturbance would result in the intrusion into awareness of aspects of the environment not normally perceived (a phenomenon we shall term "overattention"), as reported, for example, by patients in McGhie & Chapman's (1961) study and noted by Matussek (1952). Two of the quotations in Table 1 (1 and 3) clearly indicate that cognitive performance is disrupted by the intrusion of material that is normally below awareness. The others can be related to a weakening of the influence of spatial and temporal regularities on perception.

Table 1. *Current views on the nature of schizophrenics' cognitive impairment*

1. "The basic cognitive defect . . . is an awareness of automatic processes which are normally carried out below the level of consciousness" (Frith 1979, p. 233)
2. "There is some suggestion that there is a failure of automatic processing in schizophrenia so that activity must proceed at the level of consciously controlled sequential processing" (Venables 1984, p. 75)
3. Schizophrenics "concentrate on detail, at the expense of theme" (Cutting 1985, p. 300)
4. Schizophrenics show "some deficiency in perceptual schema formation, in automaticity, or in the holistic stage of processing" (Knight 1984, p. 120)
5. Schizophrenics show a "failure of attentional focusing to respond to stimulus redundancy" (Maher 1983, p. 19)
6. "Schizophrenics are less able to make use of the redundancy and patterning of sensory input to reduce information processing demands" (Hemsley 1987)
7. Schizophrenics "do not maintain a strong conceptual organization or a serial processing strategy . . . nor do they organize stimuli extensively relative to others" (Magaro 1984, p. 202)

How might these views be brought together and linked to the abnormal experiences characteristic of schizophrenia? In a very general sense, the models of Broadbent, Schiffrin, and Schneider, and Posner and his colleagues may be seen as illustrating the way in which the spatial and temporal regularities of past experience influence the processing (and, more speculatively the awareness) of current sensory input. It was therefore argued (Hemsley 1987a) that it is a weakening of the influence of stored memories of regularities of previous input on current perception that is basic to the schizophrenic condition. A related position has recently been put forward by Patterson (1987), who suggests that there is "a failure in the automaticity with which prior experience may be recreated in parallel with current stimulus input in schizophrenia (with concomitant failures in future orientation or contextually generated expectancy)."

The application of this view to the phenomenon of overattention is straightforward: There is a weakening of the capacity to select for cognitive processing only those stimuli that, given past experience of similar contexts, are relevant. Note, however, that this statement begs the question of what constitutes "relevance." The most obvious way to remedy this deficiency is to define relevance in terms of the subject's current "plans" (Miller et al. 1960) or "motor programs" (these being defined broadly to cover all action plans, including those in the purely cognitive sphere, such as the selection of stimuli for attention or the programming of streams of speech or thought), established and guided by positive instrumental reinforcement in a manner considered in more detail below. And, as we shall see, it is precisely at this point that Frith's account of positive schizophrenic symptoms comes into play.

A similar approach can be adopted with regard to thought disorder: Failure to integrate current contextual information with stored information relevant to such contexts will weaken moment-by-moment associations between the elements of the stream of discourse, allowing the occurrence of abnormal associations, and so forth. In this case, however, the importance of taking the subject's ongoing motor program into account is much clearer than in the overattention case, because it is precisely deviations from a (presumed) intended motor program that pick out the abnormalities of discourse that constitute thought disorder.

The least satisfactory application of Hemsley's hypothesis is to hallucinations. Concerning these, he writes: "In a general sense, hallucinations may be seen as intrusions into conscious experience of material from long-term memory, this then being attributed to an external source" (Hemsley 1987). He then goes on to attribute the ease with which such intrusions take place in schizophrenics to the lack of structure that, owing to their defective pigeonholing, characterises their sensory experience. In consequence, ambiguous messages may reach awareness and therefore fail to inhibit the emergence of material from long-term memory (LTM). In a similar vein, George and Neufeld (1985, p. 268) refer to an interaction between "the spontaneous retrieval of information stored in LTM and sensory processing, the latter having an inhibitory effect on the former." Rund (1986, p. 532) has also argued that "schizophrenics, possibly because of a sensory overload . . . are more susceptible to such a direct flow between long-term storage and the sensory storage level."

Both Hemsley (1987a) and Frith in his earlier formulation (1979) propose that delusions may be built up, not only on the basis of hallucinatory experiences, but also as a result of the capture of attention by incidental details of the environment. Normally, such an aspect of the situation would not reach awareness; but its registration prompts a search for reasons for its occurrence. Anscombe (1987) has extended this to suggest that certain of the patient's thoughts may be imbued with a significance that is out of proportion to their real importance simply because they happen to capture the attentional focus. He goes on to argue that both internally and externally generated perceptions "are not placed in a context of background knowledge" and that this "results in the coming to awareness of hasty and alarming appraisals by preattentive processes" (op. cit., p. 256). Anscombe's position is clearly similar to the suggestion made in the previous section that the core abnormality in schizophrenia is a weakening of the influence of the regularities of past experience on current perception; and Matussek (1952) has argued that the extent to which the context is loosened is crucial in determining the severity of the disorder.

Matussek suggested that when perceptual context is disturbed the question arises as to whether other contextual relationships may be found, quoting a patient as saying, "Out of these perceptions came the absolute awareness that my ability to see connections had been multiplied many times over" (op. cit., p. 96). Objects sharing certain qualities that had become prominent were seen as being linked in some significant way. A patient of Hemsley's, recalling his psychotic experiences, noted that the co-occurrence of two events often led immediately to an assumption of a causal relationship between them. It was as if previous non-co-occurrences were completely ignored. In reviewing the processes that

underlie the judgment of causation, Einhorn and Hogarth (1986, p. 5) note that normal people engage in causal reasoning "in order to make sense of the world," and that this is more likely to happen "when perceptions violate expectations" and become prominent. In assessing the strength of the causal relationship between X and Y, account is taken of instances of the occurrences of X in the absence of Y, and of Y in the absence of X (i.e., past regularities). If the effect of these is weakened, a stronger causal relationship between X and Y may be perceived.

Frith's (1987) account of schizophrenic psychopathology (to which we now turn) centres on the role of motor programming. His model is illustrated in Figure 1. He distinguishes between two routes to action. In the first (*stimulus intention*, i.e., SI in Figure 1), a stimulus is perceived by the subject, and then "in consultation with long-term memory the subject decides what implications the stimulus has for action." This formulation is very close to Broadbent's and Hemsley's views of the role of pigeonholing. But, according to Frith, this process is not disturbed in schizophrenia. Instead, it is the second route to action (*willed intention*, i.e., WI in Figure 1) that is disturbed. This route "starts with the subject having a plan or goal. In consultation with long-term memory, the subject decides what action is appropriate to this goal." In addition to these components in Frith's conceptual nervous system, there is a monitor, also depicted in Figure 1. This has two important functions. "First, it can detect mismatch between intentions and actions at a very early stage, thus permitting rapid error detection." Second, it "maintains the distinction between willed intentions and stimulus intentions." It is specifically the link from willed intentions to the monitor that, according to Frith's model, is disrupted in schizophrenia (Figure 1). This disruption should have the consequence that schizophrenics would have difficulty in the rapid detection and correction of what Frith calls "willed errors," i.e., those in which an action, initiated by the willed intention route, is inappropriate to current environmental demands. Frith and Done (1989) have provided experimental evidence in support of this prediction.

Frith (1987) applies this model to the primary positive symptoms of acute schizophrenia by supposing that these derive from the occurrence of what are in fact willed actions but that, because of loss of the link from WI to the monitor (Figure 1), are not recognized by the schizophrenic as such. This formulation gives rise at once to an explanation for one specific positive symptom, namely, that of the "made" volitional act, one that (even though it appears to be a normal willed act) feels to the patient as though it has occurred independently of volition. Provided one treats thought and internal speech (as Frith does) as acts of willed intention that result from the same structures and processes as normal motor acts, but without immediate expression in overt behavior, one can also account for other positive symptoms. These include *thought insertion*, in which the patient feels as though his thoughts are of alien provenance, and most important, the classic symptom of auditory hallucinations with verbal content. "The experience of thoughts being initiated without any apparent intention to have them would be described by the patient as thought insertion. Alternatively, if his normal thought processes took the form of inner speech, he might describe the experience as hearing voices inside his head" (Frith 1987; cf. Hoffman 1986). Frith also applies his hypothesis to the attentional abnormalities observed in schizophrenics, supposing that the selection of stimuli to be attended to is also an (unrecognised) willed intention; this part of his argument is less convincing, however.

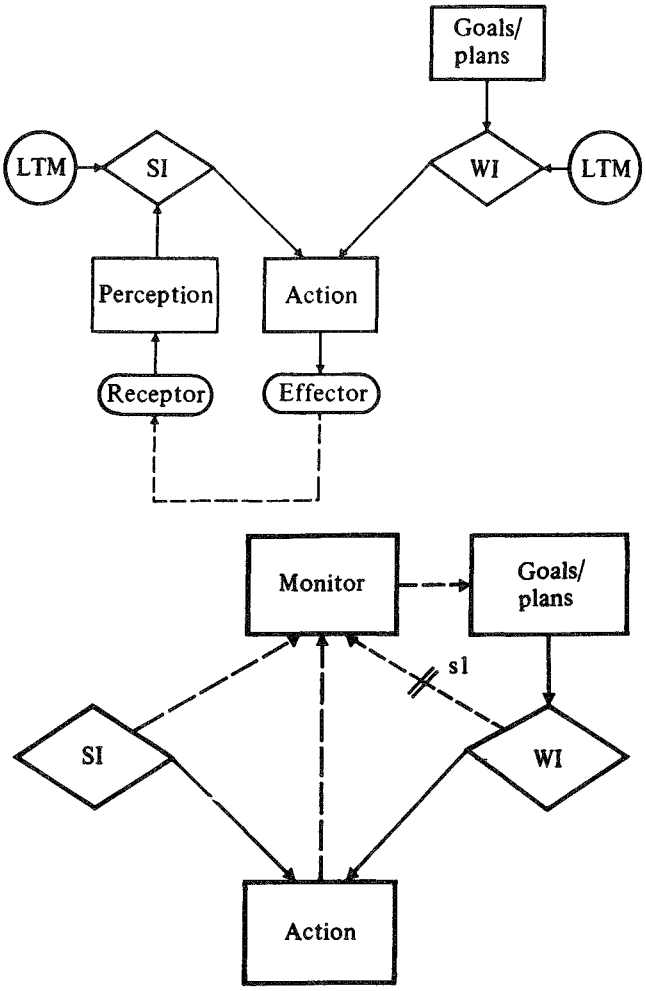

Figure 1. Frith's (1987) model of schizophrenic psychopathology. Above. An action can be elicited via two routes: (1) On the basis of current goals/plans and in consultation with long-term memory a willed intention is formed that can lead to an appropriate action. (2) On the basis of an external stimulus and in consultation with long-term memory, a stimulus intention is formed that can lead to an appropriate action. Below. In Type I (acute) schizophrenia, willed intentions are no longer properly monitored. As a consequence, actions can occur without any awareness of what elicited them. The action may then be experienced as (a) emanating from somewhere else (e.g., hallucinations), (b) being initiated by some external agency (e.g., thought insertion, delusion of passivity), or (c) being the consequence of an unassociated stimulus (e.g., delusion of reference). WI, willed intention; SI, stimulus intention; LTM, long-term memory; ---, feedback; sl, schizophrenic lesion. From Frith (1987).

Although the present target article is primarily concerned with models of positive symptomatology, we must consider briefly the issue of negative symptoms. It is at present unclear whether the distinction between positive and negative symptoms represents (a) two underlying and distinct disorders, (b) differing severity of the same disorder, (c) individual differences in reaction to the same

disorder, (d) different stages of the same disorder (acute vs. chronic), or a combination of (b), (c), and (d). Thus, Pogue-Geile and Harrow (1988, p. 437) conclude that the evidence is supportive of the view that negative symptoms "may represent a severity threshold on a continuum of liability to schizophrenia." Relevant to (c) is Strauss's (1987, p. 85) argument that certain aspects of schizophrenics' functioning may reflect the action of control mechanisms that "involve conscious and unconscious psychological processes that focus on regulating the amount of demand faced to fit the adaptive capacity available."

Although there are marked individual differences in the course of schizophrenic symptoms, there is a tendency for positive symptoms to decrease and negative symptoms to become more prominent over time (e.g., Pfohl & Winokur 1982). Hemsley (1977) argued that the pattern of cognitive deficits shown by schizophrenics might usefully be seen as resulting in a state of "information overload," and that the strategies of processing used by normal subjects in situations of experimenter-induced overload could be relevant to an understanding of schizophrenic behavior. In particular, it was proposed that certain of the negative symptoms of schizophrenia – such as social withdrawal, poverty of speech, and retardation – might for certain individuals represent adaptive strategies learned over time so as to minimize the effects of the cognitive impairment. It may also be speculated that the search for meaning in the altered experiences may diminish over time, as actions based on this prove ineffective or counterproductive. As Anscombe (1987, p. 254) puts it, "less and less the subject forms his own impressions, and more and more he is impinged upon by his environment."

In addition to chronicity, at least three factors might be expected to influence the control mechanisms used, and hence the form of behavioural abnormality. First, there are such individual differences independent of the psychosis as personality and intelligence; for example, Frith (1979) notes that premorbid intelligence may influence a subject's ability to construct the complex belief system necessary to explain all the irrelevant percepts of which he becomes aware. Second, there is the severity of the impairment; thus Knight et al. (1986) have reported that, within a schizophrenic group, ratings of attentional impairment demonstrated the best prognostic utility, predicting outcome in several domains over a seven-year period. Hemsley (1977) similarly pointed out that it may be possible to maintain a stable delusional system in the face of limited intrusions of percepts into awareness, but that beyond a certain level this may be replaced by the more transient belief systems of the nonparanoid schizophrenic. Depue and Woodburn (1975, p. 89) have also commented on "the disappearance of paranoid symptoms with chronicity." Finally, there are environmental influences: It is possible that the most acceptable methods of adaptation in many settings involve withdrawal and under-responsiveness.

2. Brain dysfunction in schizophrenia

Whatever the psychological dysfunction in acute schizophrenia (and whatever its origin – genetic or environmental, birth trauma or faulty mothering), it must reflect an equivalent neural dysfunction. We accordingly consider likely candidates for this neural dysfunction next.

The evidence implicating dopaminergic hyperactivity in schizophrenia, as well as the problems with this hypothesis, have been rehearsed many times (e.g., Carlsson 1988; Swerdlow & Koob 1987a). Here we need do no more than recapitulate the main points in favor of the hypothesis. These are: the good correlation between the antipsychotic and dopamine-receptor blocking activities of neuroleptic drugs; the capacity of indirect dopamine agonists, such as amphetamine and cocaine, to give rise to or exacerbate psychotic behaviour; and reports of elevated numbers of dopamine D2 receptors in schizophrenic brains, both postmortem (Owen et al. 1978; Seeman et al. 1984) and in vivo (Wong et al. 1986), though it is uncertain whether this finding is due to neuroleptic medication or can also be seen in the brains of unmedicated patients (Farde et al. 1987; Reynolds 1987; Wong et al. 1986). Morphological studies of the schizophrenic brain, however, have failed to reveal any obvious abnormalities either in regions that are rich in dopaminergic cell bodies (i.e., the substantia nigra, origin of the nigrostriatal pathway; and the adjacent nucleus A 10 in the ventral tegmental area, origin of the mesolimbic and mesocortical pathways); or in regions rich in dopaminergic terminals (i.e., the caudate-putamen or *dorsal striatum*, innervated by the nigrostriatal tract; and the nucleus accumbens or *ventral striatum*, innervated by the mesolimbic pathway). In contrast, there is now good evidence both of neuronal loss and of abnormalities of neuronal morphology and packaging in several regions of the temporal lobe, including the parahippocampal gyrus, the hippocampal formation, the cingulate cortex, and the amygdala (Beckmann et al. 1987; Bogerts et al. 1985; Brown et al. 1986; Falkai & Bogerts 1986), as well as a report of deceased kainate binding in the (left only) hippocampus (Kerwin et al. 1988). Following Stevens (1973), what is needed, therefore, is some way of linking dopaminergic hyperactivity with temporal lobe pathology.

Recent anatomical studies in experimental animals, allied to neurochemical observations of postmortem schizophrenic brains, have provided at least one such link; it is this link that serves as the major starting point for the specific hypotheses concerning the neural basis of schizophrenic symptoms proposed in this article. Structurally, the relevant connection is the projection from the hippocampal formation to the ventral striatum (i.e., the nucleus accumbens and the bed nucleus of the stria terminalis, which we shall henceforth refer to collectively as n. accumbens). This projection was first given a detailed description by Kelley and Domesick in 1982. The cell bodies from which it originates are pyramidal neurons located in the ventral subiculum (Kelley & Domesick 1982; Lopes da Silva et al. 1984; Totterdell & Smith 1986; Yang & Mogenson 1987a). These cells receive a synaptic input from neurons that are immunoreactive for cholecystokinin (CCK) (Totterdell & Smith 1986). The concentration of this neuropeptide has been shown to be reduced in the temporal lobe (hippocampus, amygdala, and temporal cortex) of schizophrenic brains (Roberts et al. 1983). Studies of the electrophysiological action of CCK indicate that it causes depolarization accom-

panied by a marked increase of excitability of pyramidal neurons (Dodd & Kelly 1981; Phillis & Kirkpatrick 1980), suggesting that it acts as an excitatory transmitter. This inference must be treated with some caution because CCK has been shown to be colocalised with the inhibitory transmitter, gamma-aminobutyric acid (GABA), in many hippocampal neurons (Somogyi et al. 1984). If the inference is accepted, however, it implies that, in the schizophrenic brain, there is a loss of excitatory drive onto the subiculo-accumbens projection.

Work in Smith's laboratory has recently provided a detailed description of the terminals of this projection (Freund et al. 1984; Totterdell & Smith 1989). These can be seen to innervate medium-sized densely spiny (Spiny I) neurons in n. accumbens; the Spiny I cells are known to be GABAergic and to project to the ventral pallidum (Swerdlow & Koob 1987a). This group of neurons also receives a dopaminergic projection from A10. Moreover, the findings in Smith's laboratory show that the subicular and dopaminergic inputs to n. accumbens converge on the same neuron. It is likely that the subicular projection is excitatory, its transmitter being one of the excitatory amino acids, probably glutamate (Lopes da Silva 1984; Swerdlow & Koob 1987a). It remains controversial whether dopamine acts as an inhibitory or an excitatory transmitter, but the bulk of the evidence (Swerdlow & Koob 1987a) favours an inhibitory role. Such a role is also supported by our own anatomical observations (Freund et al. 1984; Totterdell & Smith 1989). These indicate a location for the dopaminergic input on the necks of dendritic spines; a location of this kind would allow a highly selective inhibition of excitatory inputs onto the same spine (Figure 2). Yang and Mogenson (1987) have made an important finding in demonstrating, both electrophysiologically and behaviourally, that increased dopaminergic transmission in the nucleus accumbens indeed reduces the effects of stimulation of the subiculo-accumbens pathway and that this inhibitory effect of intra-accumbens dopamine release is mediated by dopamine D2, and not by D1, receptors. Recall in this connection the evidence that D2 receptor density is elevated in the schizophrenic brain (Owen et al. 1978; Seeman et al. 1984). According to Wong et al.'s (1986) observations in vivo applying positron emission tomography to drug-naive patients, this abnormality is present in particular in the striatum (it was not possible to distinguish between dorsal and ventral striatum); this finding was not replicated in Farde et al.'s (1987) similar study, however.

Here, then, is one realistic possibility for the origin of the combination of limbic pathology and dopaminergic hyperactivity that would appear to characterise schizophrenia, namely, a disruption of the normal interaction between (1) a subicular excitatory glutamatergic input, and (2) an A10 inhibitory dopaminergic input onto the same Spiny I GABAergic efferents from n. accumbens (Totterdell & Smith 1989). (This type of interaction, and its possible relation to schizophrenia, has been discussed by Carlsson [1988]; our focus on the subiculo-accumbens and A10-accumbens projections may be regarded as a specific instance of the proposals he considers in more general terms.)

There are other possible interactions between the subicular glutamatergic and A10 dopaminergic afferents to n. accumbens, however. Studies with a variety of

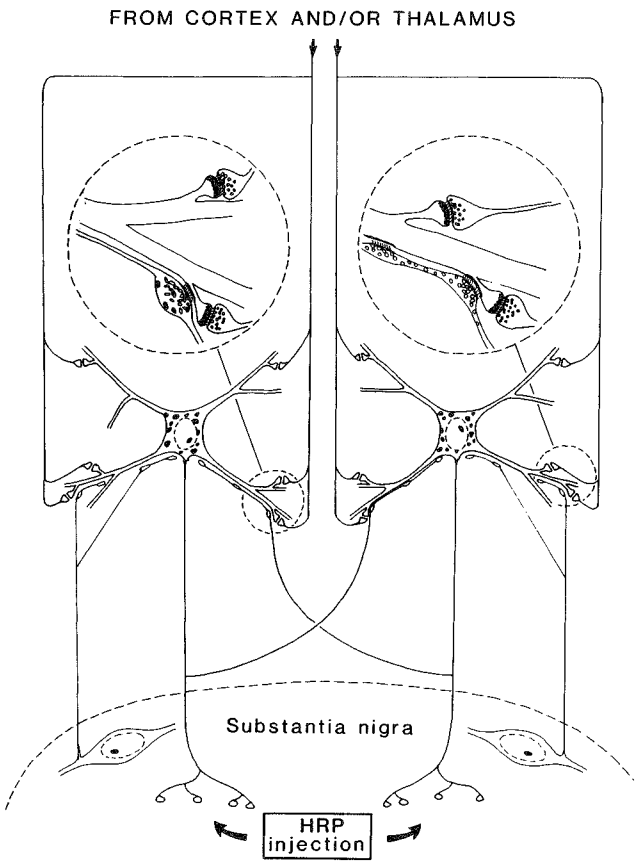

Figure 2. A diagrammatic summary of the synaptic connections of striatonigral neurons identified by Freund et al. (1984). The nigrostriatal cells immunoreactive for tyrosine hydroxylase (TH, a marker of dopaminergic function) are blue, the axons of striatonigral neurons labelled retrogradely by horseradish peroxidase (HRP) are red (including the local axon collaterals). The outline of the medium sized spiny cells and their cortical and/or thalamic input, is drawn in black. The TH-immunostained fibres, containing large, nearly round vesicles, are in synaptic contact with the necks of spines, proximal and distal dendritic shafts, and perikarya of the striatonigral neurons. There also seems to be an interplay between striatonigral neurons via their local axon collaterals, labelled by transported HRP granules (red). They make synaptic contacts on the same postsynaptic targets as the TH-immunoreactive axons, but with a much higher frequency on proximal dendritic shafts and perikarya. From Freund et al. (1984); as reported by Totterdell and Smith (1989), similar arrangements appear to hold for the nucleus accumbens.

techniques have demonstrated that glutamate enhances dopamine release from dopaminergic terminals in both the dorsal corpus striatum and n. accumbens and that in the dorsal striatum (there appear to be no equivalent data for n. accumbens) dopamine inhibits glutamate release from glutamatergic terminals (Cheramy et al. 1986; Chesselet 1984; Marien et al. 1983; Romo et al. 1986). The combination of these two effects provides a potential mechanism by which the point-to-point glutamatergic afferents to the basal ganglia could activate a specific set among the otherwise widely ramifying dopaminergic afferents to the same regions, so localising the inhibitory effects of the latter, dopaminergic, projection to a particular group of synapses (Glowinski et al. 1984).

We shall consider later what psychological functions

might be discharged by these various interacting inputs to n. accumbens. At the physiological level, what changes might one expect in dopaminergic transmission in n. accumbens if (as we suppose to be the case in schizophrenia) there were a reduction in the strength of the subicular excitatory input to this structure? And how might such changes result in the kind of increase in dopaminergic activity that appears to characterize at least the acute phase of schizophrenia? Two ways in which this might happen are as follows.

First, let us suppose that the net output from n. accumbens reflects a balance between the inputs it receives from the subiculum and A10, respectively. Then loss of the former would be functionally equivalent to an increase in the effect of the latter, dopaminergic input. We have observed effects consistent with this expectation in our own laboratory: Hippocampal aspiration increased dopaminergic activity (measured ex vivo as the ratio of the two chief metabolites of dopamine, dihydroxyphenylacetic acid, DOPAC, and homovanillil acid, HVA, to the parent amine) at 28, but not 7, days after the lesion, and in n. accumbens but not in the dorsal striatum; similar but less pronounced effects were seen after partial section of the projection from subiculum to n. accumbens (Mitchell et al., unpublished data).

Second, given the observations in Glowinski's laboratory of an excitatory effect of glutamate upon dopamine release (see above), one might expect just the opposite result: a reduction in dopaminergic transmission. An effect of this kind has also been reported after hippocampal aspiration: In n. accumbens (but not in the dorsal striatum) there was a reduction in dopamine use, this effect being observed at 7 but not 28 days after the lesion (Springer & Isaacson 1982). These authors also report an up-regulation of accumbens dopamine receptor binding 28 days after hippocampectomy, whereas we observed a (nonsignificant) decrease. The reasons for the discrepancy between Springer & Isaacson's results and our own are unknown. Both sets of data agree, however, in showing that damage to the hippocampal formation alters dopaminergic transmission in n. accumbens, and both may indicate a functional increase in such transmission (increased dopamine utilisation ratio in our experiments, up-regulation of dopamine receptor binding in Springer and Isaacson's). Springer & Isaacson's results are congruent with the reports of increased dopamine receptors in schizophrenia (Owen et al. 1978; Seeman et al. 1984; Wong et al. 1986); though (as already noted) the role of neuroleptic medication in the latter finding is still uncertain (Farde et al. 1987; Reynolds 1987).

3. Some recent experiments with animals

The above arguments can be used to provide a number of points of reference against which to test animal models of schizophrenic psychological dysfunction. They suggest psychological, pharmacological, and neuropathological criteria that must be met in any adequate model. Psychologically, the dysfunction should have appropriate cognitive features, as suggested, for example, by Hemsley's (1987a) or Frith's (1987) analyses of the symptoms of acute schizophrenia. Pharmacologically, it should be possible to produce the dysfunction by enhancing dopaminergic transmission in n. accumbens and to reverse the effect by administering a neuroleptic dopamine-receptor blocking drug. Neuropathologically, it should be possible to induce an equivalent dysfunction by damaging the cells that are the source of the subicular input to n. accumbens, or by directly sectioning the pathway itself; it is not yet clear whether the behavioural consequences of the latter manipulations should be evident in the short or only in the long term, but in either case they too should be reversible by treatment with neuroleptics. (Consistent with the latter inference, though in an inappropriate behavioural paradigm, it has been reported that the hyperactivity and hyper-responsiveness observed in the rat after large hippocampal lesions can be reduced by neuroleptics; Isaacson 1980.) We describe in this section some recent experiments that bear on these points; we believe these experiments to be of interest, not only for their actual results, but also as illustrations of a valuable general approach to the neuropsychology of schizophrenia.

The experiments have focussed on three behavioural phenomena, all of which were selected so as to comply with the first, psychological, requirement of having appropriate cognitive features. They are latent inhibition (Lubow 1973; Lubow et al. 1982), Kamin's (1968) blocking effect, and the partial reinforcement extinction effect (PREE [Gray 1975]). Each of these can be regarded as instances of the "influence of stored memories of regularities of previous input on current perception" (Hemsley 1987a), or, in the case of the PREE, on motor programming; thus, they each have face validity as models for the cognitive disorder that we earlier suggested might underlie acute schizophrenia.

The basic paradigm for the demonstration of latent inhibition consists of two groups of subjects, one preexposed to a stimulus to which both groups must subsequently form an association; the pre-exposed group is slower to learn the association, having learned not to attend to the pre-exposed stimulus because it initially signalled nothing of importance. Many different paradigms have been used to demonstrate latent inhibition in a wide range of species (Lubow 1989). The data most relevant to the present paper have been gathered with rats in two particular paradigms. In the first (e.g., Weiner et al. 1984), the measure of learning is conditioned suppression of drinking; the conditioned stimulus (CS) is a tone that has been paired with footshock "off the baseline" (i.e., when the animal is not drinking) according to standard Pavlovian procedures. The pre-exposed group is presented with the tone (e.g., 30 times), with no further consequence, before conditioning ever starts. This pre-exposure to the tone has the effect that, when it is presented to the animal after conditioning, the degree of conditioned suppression of drinking is reduced relative to animals to which the tone is first presented during the conditioning phase of the experiment. The experiment can be run with all three phases (pre-exposure, conditioning, test) on the same day, or each separated by, for example, 24 hours. The second paradigm uses as a combined conditioning and test phase the acquisition of a shuttling response to avoid shock (signaled by a tone) in a two-compartment box (e.g., Solomon et al. 1981; Weiner et al. 1988); again, pre-exposure of the tone leads to impaired learning, in this case, slower acquisition of the shuttling response. No particular element in these para-

digms is critical; for example, a light can be used instead of a tone, or appetitive learning (to obtain food) instead of shock-motivated learning (Lubow 1989).

In Kamin's blocking effect, there are again two groups of subjects, one preexposed to a first association between a conditioned stimulus (CS1) and an unconditioned stimulus (UCS). Both groups are then presented with a compound stimulus, CS1 + CS2, followed by the same UCS, and finally tested for their response to CS2; the pre-exposed group learns less about CS2, this learning being "blocked" by the prior association between CS1 and the UCS. The Kamin blocking effect has been widely used in the analysis of associative learning and the role played in this by selective attention; the data thus gathered have formed the basis of several important theories (see, e.g., Dickinson 1980; Wagner & Rescorla 1972). The most widely used paradigm uses (with rats) a shock UCS, tone and light as the two CSs (counterbalanced so that each serves as CS1 and CS2 for different subgroups), and conditioned suppression (often of bar-pressing for food reward) as the measure of associative learning. Again, however, as in the case of latent inhibition, none of these elements is critical, and a wide variety of other species, CSs, UCSs and measures of learning, in various combinations, have been used (Mackintosh 1983).

In the PREE, two groups learn a rewarded instrumental response, one being given only rewarded trials (continuous reinforcement, CRF), the other rewarded and nonrewarded trials randomly interspersed (partial reinforcement, PRF). The two groups are then tested to see how long they persist in responding when no more rewards are delivered (*extinction*); the PRF group is more resistant to extinction, having learned to ignore nonreward in a manner analogous to the way in which animals learn to ignore the preexposed stimulus in the latent inhibition paradigm. The most commonly studied paradigm involves rats that run in a straight alley for food reward. Such variables as the size of the reward, number of acquisition trials, intertrial interval, percentage of rewarded trials in the PRF condition, and so on, can take on widely differing values without eliminating the PREE, though somewhat different processes appear to mediate the phenomenon depending upon these parameter values (see, e.g., Feldon et al. 1979; Mackintosh 1983). The PREE, too, has been demonstrated in many other species and with many other instrumental responses.

In accordance with the view we have been developing, behavioral studies in animals have shown that each of these phenomena is abolished by the dopamine-releasing psychotomimetic drug, amphetamine (Crider et al. 1982; Solomon et al. 1981; Weiner et al. 1981). Moreover, the additional requirement that these effects should be reversed by administering neuroleptic dopamine-receptor blocking drugs is also met: The effects of amphetamine on latent inhibition (Solomon et al. 1981) and the Kamin effect (Crider et al. 1982) can be reversed by treatment with neuroleptics. Furthermore, in each case the amphetamine effect takes the predicted direction (i.e., one of overattention) on the hypothesis that the drug is indeed acting inter alia as a psychotomimetic. Thus, in the latent inhibition paradigm, the pre-exposed group treated with amphetamine learns faster or better than placebo-treated controls, whereas the non-pre-exposed group is unaffected by the drug; similarly, in Kamin's blocking paradigm, the amphetamine-treated blocked group learns the CS2-UCS association better than placebo-treated controls; and, in the PREE, the drug-treated PRF group responds more to the nonrewarded trials of extinction (i.e., extinguishes faster) than the placebo PRF controls (but no differences in extinction rates are seen between drug and placebo CRF groups, so the drug does not simply speed up extinction as such). In all three cases, therefore, one could say, in accordance with Hemsley's (1987a) view, that the amphetamine-treated animals behave as though their current perception (of the pre-exposed stimulus; of the relationship between CS1, CS2, and the UCS; or of nonreward) were less controlled than normal by experience of previous regularities of input. (We do not know of any experimental paradigms with animals that relate so well to Frith's concept of the monitoring of willed intentions. Paradigms of this kind would be extremely useful.)

Given that functional dopamine overactivity involves what we called "overattention," the question arises as to what behavioural effects would result when neuroleptics are administered to normal individuals. One possibility is that there could be a drug effect opposite to that of amphetamine; the other is that the neuroleptics will only have an effect if the dopamine system is already overactive. Experimental analysis of this issue makes it clear that neuroleptics do have behavioural effects on performance in these tasks by normal animals that are the opposite of the effects of amphetamine. Thus, haloperidol treatment produces latent inhibition after only 10 exposures (Weiner & Feldon 1987); enhances latent inhibition after 40 exposures (Feldon & Weiner 1988; Weiner & Feldon 1987; Weiner et al. 1987c); and gives rise to a larger PREE (Feldon et al. 1988) than is seen in controls. As the dopamine system moves from functional hypoactivity through to hyperactivity, so learning to disattend in these tasks changes from more to less efficient than normal.

An effect of amphetamine on animal behaviour makes a *prima facie* case that the behaviour in question is relevant to schizophrenia. This case, however, is much weaker when the behaviour has no obvious parallels in schizophrenic symptomatology, thus failing to meet our first, psychological criterion (Gray & Baruch 1987). Our hypothesis clearly requires, however, that disruption of the subiculo-accumbens projection should have essentially the same consequences as amphetamine administration in the same behavioral tests. A second, neuropathological line of evidence therefore comes from experiments in which large hippocampal lesions have been used to destroy the source of this projection (together, however, with a variety of other projections that are equally disrupted by hippocampectomy). Experiments of this kind have shown that latent inhibition (Kaye & Pearce 1987), Kamin's blocking effect (Solomon 1977) and the PREE (Jarrard et al. 1986; Rawlins et al. 1980) are all disrupted by damage to the hippocampal formation.

Given the arguments developed above, we would clearly wish to interpret the effects of amphetamine on these three forms of behaviour as reflecting the release of dopamine in n. accumbens; the effects of hippocampal damage would reflect disruption of the projection to n. accumbens from the subiculum. These hypotheses need to be tested in greater detail.

One issue is whether the effects of systemic manipulations of dopamine can really be attributed to a specific action on n. accumbens. Solomon and Staton (1982) have indeed provided evidence that the effect of amphetamine on latent inhibition is specifically because of an action on dopamine receptors in n. accumbens rather than the caudate; microinjections of the drug into the former, but not the latter, structure eliminated latent inhibition. This result is supported by the observation (Weiner, Izraeli-Telerant & Feldon 1987f) that latent inhibition is eliminated by a low (1.5 mg/kg) but not a high (6 mg/kg) systemic dose of amphetamine, given other evidence (Kelly et al. 1975) that low doses of this drug preferentially cause dopamine release in n. accumbens, whereas high doses do so preferentially in the caudate-putamen. As we shall see, this dose effect provides a tool with which to investigate comparable phenomena in man. A further congruent finding (though so far only preliminary; Clark et al., unpublished data) is that destruction of the dopaminergic terminals in n. accumbens (by local injection of the catecholamine-specific neurotoxin, 6-hydroxydopamine, 6-OHDA) appears to increase the magnitude of latent inhibition by further retarding learning in the pre-exposed animals.

Another issue is whether the effects of hippocampal lesions can safely be attributed to destruction of the subicular projection to the accumbens, or whether they result from destruction of quite different hippocampal system projections. Rawlins et al. (1989) have recently shown that the PREE is abolished by a very restricted knife cut that partially severs the subiculo-accumbens projection while causing minimal damage to other hippocampal output pathways; this provides strong evidence for a critical role of the subiculo-accumbens projection. More such experiments are needed to ensure that what is true for the PREE also holds for latent inhibition and the Kamin effect; subsequent experiments will then need to demonstrate that these more specific effects are themselves reversible by appropriate pharmacological treatments, for example, neuroleptics.

Other evidence, although in no way incompatible with a critical role for the subiculo-accumbens projection, throws a rather different light on hippocampal involvement in latent inhibition. As shown by Solomon et al. (1978; 1980), latent inhibition is abolished by systemic injection of parachlorophenylalanine, a drug that depletes central stores of serotonin; it is also eliminated by electrolytic lesions of the median raphe (which supplies serotonergic afferents principally to the hippocampal formation) but not the dorsal raphe (origin of the serotonergic afferentation of other forebrain regions). This involvement in latent inhibition of the serotonergic system has been confirmed by Cassaday et al. (in press): A range of drugs that reduce serotonergic activity reduced or abolished the effects of pre-exposure. Cassaday has further demonstrated that local injection of the indoleamine-specific neurotoxin, 5,7-dihydroxytryptamine, into the fornix-fimbria, selectively destroying serotonergic afferents to the hippocampus, abolishes latent inhibition, a result that contrasts sharply with the failure of 6-OHDA-induced lesions of the noradrenergic innervation of the septohippocampal system to affect this behaviour (Tsaltas et al. 1984).

These findings suggest that exclusive disruption of serotonergic function in the hippocampal formation is sufficient to eliminate latent inhibition. This inference does not conflict with our earlier arguments implicating the subiculo-accumbens projection and the dopaminergic innervation of n. accumbens, because the serotonergic input to the hippocampus is presumably upstream to these. Indeed, it offers a way to reconcile the dopaminergic hypothesis of acute schizophrenia with the second major neurochemical interpretation of this condition, namely, that it reflects serotonergic under-activity. This "serotonergic" hypothesis is less firmly grounded than its dopaminergic counterpart, being based principally on the hallucinogenic properties of drugs like lysergic acid diethylamide (LSD) (which reduces the firing of serotonergic neurons by acting as a cell-body autoreceptor agonist; Haigler & Aghajanian 1973), though there is experimental evidence also in its favor (Claridge 1978). If, as appears to be the case, the overattention demonstrated in loss of latent inhibition can be caused by either dopaminergic overactivity or serotonergic underactivity, the two hypotheses may simply reflect two sides of the same coin.

4. Some recent experiments with human subjects

Although the behavioural tests used in these animal experiments have a more obvious face validity than, for example, tests of motor activity, the results are still open to an obvious criticism: How can such simple forms of behaviour be expected to reflect accurately the presumably much more complex cognitive processes that underlie learning and attention in human beings? Ideally, we would need to show that these same tests reveal the same sensitivity to functional activity levels in the human dopamine system. We have therefore begun to collect such data from human subjects, using all three paradigms described above. Our basic strategy is to compare acute (and therefore presumably hyperdopaminergic) schizophrenics to both chronic schizophrenics (in whom dopaminergic activity is controlled by neuroleptics) and normal subjects. We predict that the behaviour in these tests of the acute but not the chronic schizophrenics will resemble that of the amphetamine-treated rat.

We first carried this strategy through for latent inhibition. The task (Baruch et al. 1988c) is formally analogous to those used with animals, but all the details are of course different. The subject listens to a tape recording, binaurally via earphones, of a series of nonsense syllables, initially with instructions to pick out one of them and count its recurrences. This is a so-called masking task, necessary to demonstrate latent inhibition with human adults, though not children (Lubow 1989); it presumably functions to distract the subject's attention from the stimulus destined to be the CS. This stimulus consists, in our paradigm, of short bursts of low-intensity white noise superimposed (30 times), in the pre-exposure condition only, on the tape of nonsense syllables played into one ear (counterbalanced); non-pre-exposed controls hear only nonsense syllables. After the pre-exposure phase is completed, both groups of subjects are played the tape of nonsense syllables plus bursts of white noise and asked to report (by raising a hand) when they think a counter display in front of them will be increased. The increments

in fact occur immediately after each burst of white noise. It is replicably observed with normal (as well as agoraphobic) subjects that the pre-exposed subjects take substantially more trials than the nonpre-exposed controls to detect the association between noise and counterincrements (Baruch 1988a; Baruch et al. 1988c; N. S. Gray personal communication).

As predicted, however, acute schizophrenics (tested within the first two weeks of the current episode of illness) fail to display latent inhibition, though the phenomenon is present in chronic schizophrenics (Baruch et al. 1988b). The contrast between acute and chronic schizophrenics appeared both in a cross-sectional study, testing different groups of subjects, and in a longitudinal study in which the same subjects were tested twice, in the first two weeks and again six to seven weeks later. Furthermore, the loss of latent inhibition in the acute schizophrenics was due to unusually rapid learning in the preexposed group, just as it is in the amphetamine-treated rat. This pattern of results is important in that it eliminates the possibility that the loss of latent inhibition is a nonspecific consequence of the generally poor cognitive performance of schizophrenic patients, a methodological problem that has plagued research in this field. The presence of latent inhibition in the chronic schizophrenic group is most probably because of their being treated with neuroleptics, though this is difficult to demonstrate conclusively because of the impossibility, for ethical reasons, of including an untreated schizophrenic control group.

These results with schizophrenics are confirmed from studies with normal volunteers given oral amphetamine (N. S. Gray, personal communication). Two doses (5 and 10 mg) were used to determine whether the inverse dose-related effect of amphetamine on latent inhibition in the rat (Weiner et al. 1987b; see above) might hold also in man. The results bore out this expectation: the low dose, but not the high one, abolished the latent inhibition in placebo-treated controls; again, this effect resulted from improved speed of learning in the pre-exposed condition. These pharmacological similarities provide powerful evidence that, despite the enormous differences in testing procedures, latent inhibition measured in rodent and human subjects, respectively, constitutes the same phenomenon. This experiment revealed an unsuspected complication, however. Rather than simply counterbalancing the ear of presentation of the white noise, N. S. Gray (personal communication) analysed her data to see whether this variable had any effect. It turned out that, in the placebo condition, latent inhibition was present only in subjects for whom the noise was presented to the left ear; thus the effects of amphetamine described above apply only to subjects tested in this way. Given the abundant evidence for hemispheric differences in schizophrenic psychopathology (e.g., Gruzelier et al. 1988) and neuropathology (e.g., Jeste & Lohr 1989; Kerwin et al. 1988), this is an intriguing observation that clearly requires further investigation, with both normal and schizophrenic subjects.

It is also of interest that, in the same experiment, amphetamine affected a more specifically human form of cognition: the *negative priming effect*, previously shown to be abnormal in schizophrenia by Beech et al. (1989). This effect was studied by asking subjects to name one of two simultaneously presented but differently coloured (red and blue) line drawings of common objects, the correct target being defined by colour. Naming latency in the placebo condition was reliably slower if the target on trial N was the same as the distractor on trial N-1; this is the negative priming effect. The priming effect, however, was not significant after administration of 5 mg oral amphetamine, because of faster responding on the critical trials when the target consisted of the distractor on the previous trial (E. Peters, personal communication). The data obtained with the 10 mg dose were ambiguous, and these data on the negative priming effect must all be regarded as preliminary. Nonetheless, they represent a first step in linking the simple latent inhibition effect with more complex aspects of human cognitive performance (latent inhibition and negative priming were measured in the same subjects and on the same testing occasion).

Given these encouraging results with the latent inhibition paradigm, we next turned to the Kamin blocking effect. The paradigm we use (Jones et al. 1990) requires the subject in the final test phase to predict when a yellow square, interspersed over time with other colored squares, will appear on a computer monitor. In phase 1 of the experiment, in the blocking condition, the yellow square (UCS) is always preceded by a blue square (CS1); controls in this phase observe triangles of different colours, appearances of the yellow (or any other) one being unpredictable. In phase 2, both groups observe a sequence in which the yellow square is regularly preceded by the blue one, but also by a second stimulus (CS2) presented simultaneously with the blue square. Initially, we used a computer-generated noise as CS2; this worked well with normal subjects, but unfortunately chronic schizophrenics did not attain adequate levels of performance with this procedure (probably because of its cross-modal aspect). Subsequently, therefore, we used two small, white squares presented at the edges of the monitor as CS2; this procedure worked well with both normal and schizophrenic subjects. In phase 3, the blue square has a random relationship with occurrences of the yellow square, which can be predicted only on the basis of CS2 (noise or white squares). Learning is measured by the number of trials the subject takes to reach a criterion of reliable prediction (by pressing a button) of the occurrences of the yellow square; the blocking effect should appear as a delay in reaching this criterion in phase 3 as a function of exposure to the association between the blue and yellow squares in phase 1. Normal (as well as agoraphobic) subjects show the effect reliably with both procedures (Jones 1989; Jones et al. 1990).

As in the case of latent inhibition, this paradigm is formally analogous to the Kamin blocking effect as measured in animals, but completely different in all procedural details. Theories of the Kamin effect in animals have emphasized the role played by selective attention, though via a variety of different possible mechanisms (Dickinson 1980; Mackintosh 1983). If this emphasis is correct, there should be a relationship between the Kamin effect and selective attention as measured in more specifically human paradigms. A demonstration of the correctness of this prediction would be particularly important, given that theories of human selective attention (Eysenck 1982) have developed in virtually total isolation from work with animals. We therefore measured the Kamin blocking effect in normal subjects (using the

procedure described above, with noise as CS2) who also took part in two tests of incidental learning. In one of these the contrast between explicit and incidental learning was defined by words versus word position, whereas in the other it was defined by a target initial word letter versus nontarget initial letters. In both cases, subjects who showed a large Kamin effect showed only low levels of incidental learning, as predicted (Jones et al. 1990).

The key predictions for the Kamin effect are the same as for latent inhibition: It should (1) be present in chronic and absent in acute schizophrenics, and it should (2) result from better learning of the association between CS1 (white squares) and the UCS (the yellow square) in the acute group that has learned the association between CS2 (the blue square) and the UCS in the first phase of the experiment. This is indeed the pattern of results obtained by Jones (1989).

This is still a flimsy data base. Nevertheless, our results so far encourage us to believe that it is worth constructing a more specific neuropsychological model of the interactions between the septohippocampal system and the basal ganglia, if only as a guide to further research along the general lines described above. This model is presented next.

5. A limbic-striatal model: The septohippocampal system

The key assumption to which the arguments so far have led, and which the model presented here embodies, is that positive schizophrenic symptoms (notably, overattention, thought disorder, and hallucinations) arise from a disruption in the normal functioning of the input to the basal ganglia (in particular, n. accumbens) from the limbic system (in particular, the subiculum). The model incorporates both Hemsley's (1987a) notion that the schizophrenic suffers from a weakening of the influence of stored memories of past regularities on the interpretation of current perceptual input and Frith's (1987) notion that the schizophrenic suffers from a weakening of the capacity to monitor willed intentions. We show how these views can both be incorporated into a single neuropsychological model.

The main lines of the model were originally proposed in the context of a theory of the neuropsychology of anxiety (Gray 1982a), in which the septohippocampal system, together with a number of other limbic and cortical structures closely related to the septohippocampal system, were charged with a general monitoring or *comparator* function. (The application of this model to schizophrenia has independently been proposed, but with important differences in detail, by Frith & Done [1988]; we consider below the relationship between their hypothesis and the present one.)

The information-processing functions attributed to Gray's (1982a) comparator are illustrated in Figure 3. The system (i) takes in information describing the current state of the perceptual world; (ii) adds to this further information concerning the subject's current motor program; (iii) makes use of information stored in memory and describing past regularities relating stimulus events to other stimulus events; (iv) similarly makes use of stored information describing regularities relating past responses to subsequent stimulus events; (v) predicts, from these sources of information, the next expected state of the perceptual world; (vi) compares the predicted to the actual next state of the perceptual world; (vii) decides that there is either a match or a mismatch between the predicted and the actual states of the world; (viii) proceeds, if there is a match, to run through steps (i) to (vii) again; but (ix) if there is a mismatch, brings the current motor program to a halt, so as to take in further information and resolve the difficulty that has interrupted this program.

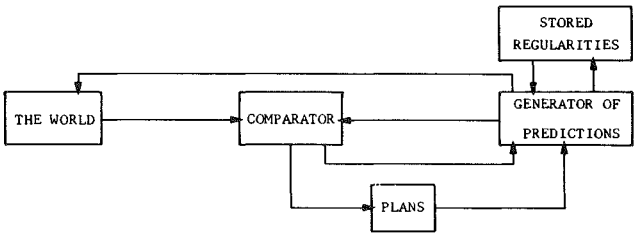

Figure 3. The information-processing functions attributed to Gray's (1982a; 1982b) comparator model of septohippocampal function.

In the application of this model to anxiety, the focus of the analysis was on step (ix) and the further consequences of this step (Gray 1982a); here we shall instead be concerned with the details of the monitoring process itself and the way this interacts with the running of motor programs. Note that the two processes each separately implicated in the origin of schizophrenic positive symptoms by Hemsley (1987a) and Frith (1987), respectively, are intertwined in Figure 1: The generation of a prediction depends on both past environmental regularities (Hemsley) and the current motor program (Frith's "willed intention").

Figure 3 depicts, as it were, the software of the comparator proposed by Gray (1982a); the corresponding hardware is illustrated in Figure 4. Details of the way this hardware is supposed to carry out the information-processing functions encapsulated in Figure 3 can be found in Gray (1982a). Here we note only the following points. First, the heart of the comparator function is attributed to the subicular area. This is postulated to receive elaborated descriptions of the perceptual world from the entorhinal cortex, itself the recipient of input from all cortical sensory association areas; to receive predictions from, and initiate generation of the next prediction in, the Papez circuit; and to interface with motor programming systems (not themselves included in Figure 4) so as either to bring them to a halt or to permit them to continue. Second, the prefrontal cortex is allotted the role of providing the comparator system with information about the current motor program (through its projections to the entorhinal and cingulate cortices, the latter forming part of the Papez circuit). Last, the system depicted in Figure 3 needs to be quantised in time to allow a comparison between specific states of the world and corresponding predictions, followed by the initiation of the next prediction and the next intake of information describing the world. This function is attributed to the hippocampal theta rhythm, giving rise to an *instant* within the model of about one-tenth of a second.

We are now in a position to rejoin the anatomical

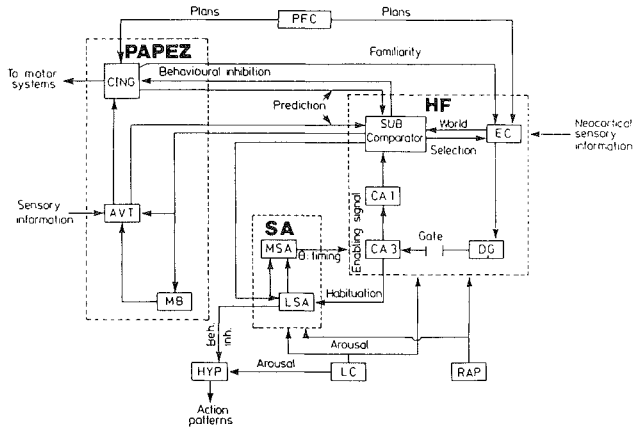

Figure 4. The septohippocampal system and other associated structures proposed by Gray (1982a;b) as discharging the functions of the comparator illustrated in Figure 3. The three major building blocks are shown in heavy print: HF, the hippocampal formation, made up of the entorhinal cortex, EC, the dentate gyrus, DG, CA 3, CA 1, and the subicular area, SUB; SA, the septal area, containing the medial and lateral septal areas, MSA and LSA; and the Papez circuit, which receives projections from and returns them to the subicular area via the mammillary bodies, MB, anteroventral thalamus, AVT, and cingulate cortex, CING. Other structures shown are the hypothalamus, HYP, the locus coeruleus, LC, the raphe nuclei, RAP, and the prefrontal cortex, PFC. Arrows show direction of projection; the projection from SUB to MSA lacks anatomical confirmation. Words in lower case show postulated functions; beh. inh., behavioural inhibition.

arguments developed earlier, for the most likely route by which the system depicted in Figure 4 can interact with motor systems is the projection from the subiculum to n. accumbens. As argued above, this is also a likely pathway by which the known pathology of the schizophrenic brain (in the hippocampal formation and related cortical regions) can interact with the ascending dopaminergic system that, on other grounds, has been implicated in the functional abnormalities of schizophrenic behaviour. In the next stage of the argument, therefore, we wish to consider how the motor programming system of which n. accumbens forms a part works, and how its working may mesh with the comparator system illustrated in Figures 3 and 4 above.

6. A limbic-striatal model: The basal ganglia

The chief building blocks of which the motor programming system is composed are illustrated in Figures 5 and 6, based on Groves (1983), Penney & Young (1981), and chiefly Swerdlow & Koob (1987a). Figure 5 shows the interrelations between nonlimbic cortex (i.e., motor, sensorimotor, and association cortices), the caudate-putamen (or dorsal striatum), the dorsal globus pallidus, nn. ventralis anterior (VA) and ventralis lateralis (VL) of the thalamus, and the ascending dopaminergic pathway from the substantia nigra; for the sake of brevity we shall refer to this set of structures as the *caudate* motor system. Similarly, Figure 6 shows the interrelations between the limbic cortex (i.e., prefrontal and cingulate cortices), n. accumbens (ventral striatum), the ventral globus pallidus, the dorsomedial (DM) thalamic nucleus, and the ascending dopaminergic projection from A10; for brevity, we shall call this set of structures the *accumbens* motor system.

As proposed by Swerdlow and Koob (1987a), one can regard both the caudate and accumbens systems as being composed of three interacting feedback loops: a cortico-thalamo-cortical positive feedback loop (I in Figures 5 and 6); a cortico-striato-pallido-thalamo-cortical positive feedback loop (II); and a striato-pallido-tegmento-striatal negative feedback loop (III), *tegmento* in this phrase referring to the substantia nigra or nucleus A10 in the ventral tegmental area. Loop I consists of a double excitatory input from cortex to thalamus and thalamus to cortex, and may therefore serve to maintain the continuous stream of impulses necessary to achieve one step (see below) in an ongoing motor program. Loop II is more complex: The cortical excitatory (glutamatergic) input onto the Spiny I inhibitory (GABAergic) efferents from the striatum should have the effect of inhibiting the further inhibitory GABAergic pathway from the pallidum to the thalamus, thus further strengthening (by disinhibition) the excitatory interactions subserved by Loop I. To bring this reverberatory excitatory activity to an end, as proposed by Swerdlow and Koob (1987a), Loop III is called into play: Excitation of the Spiny I GABAergic output from the striatum inhibits the pallidal GABAergic inhibition of the ascending dopaminergic input to the striatum, which is therefore increased. Because this dopaminergic input is itself also inhibitory, striatal activity is accordingly reduced – or rather (as proposed by, e.g., Oades [1985] and Robbins & Everitt [1982] and developed further below), it is permitted to switch from one pattern to another.

A further important anatomico-physiological feature of

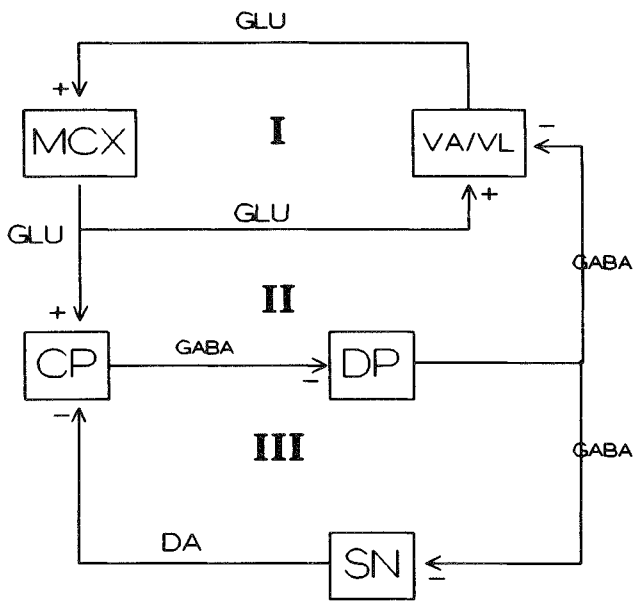

Figure 5. Nonlimbic cortico-striato-pallido-thalamic-midbrain circuitry making up the caudate motor system. MCX: motor and sensorimotor cortex. VA/VL: ventral anterior and ventrolateral thalamic nuclei. CP: caudate-putamen (dorsal striatum). DP: dorsal pallidum. SN: substantia nigra. GLU, GABA and DA: the neurotransmitters, glutamate, gamma-aminobutyric acid and dopamine. +, −: excitation and inhibition. I, II, III: feedback loops, the first two positive, the third negative. Based on Swerdlow & Koob (1987).

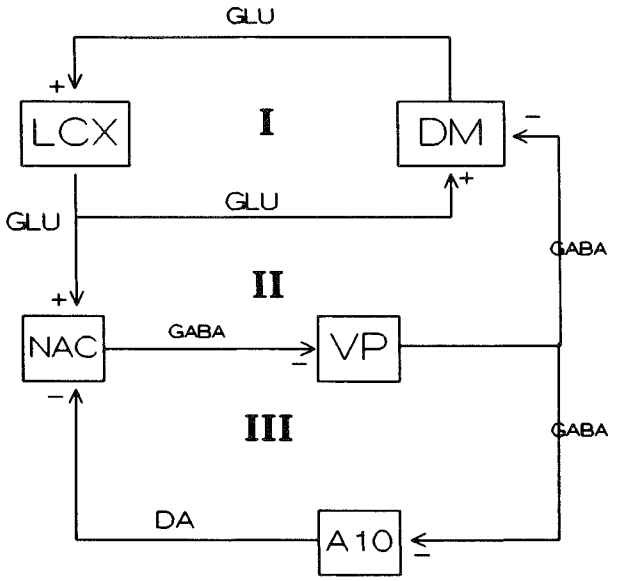

Figure 6. Limbic cortico-striato-pallido-thalamic-midbrain circuitry making up the accumbens motor system. LCX: limbic cortex, including prefrontal and cingulate areas. DM: dorsomedial thalamic nucleus. NAC: nucleus accumbens (ventral striatum). VP: ventral pallidum. A 10: dopaminergic nucleus A 10 in the ventral tegmental area. Neurotransmitters and feedback loops, as in Figure 8. Based on Swerdlow & Koob (1987).

the caudate and accumbens motor systems lies in the organisation of the Spiny I output cells (Groves 1983). These comprise about 96% of the entire population of striatal neurons. Each Spiny I cell appears to receive convergent inputs from many cortical and thalamic afferents, giving rise to the inference that these cells are "activated by the temporal coincidence of convergent excitatory input from several different sources" (Groves 1983, p. 116). Single-unit recording in behaving primates has thrown some light on the nature of these sources. As summarised by Rolls and Williams (1987, p. 37): "Neurons in the caudate nucleus, which receives inputs from the association cortex, have activity related to environmental stimuli that signal preparation for or initiation of behavioural responses . . . Neurons in the putamen, which receive inputs from the sensorimotor cortex, have activity related to movements. Neurons in the ventral striatum (including the nucleus accumbens), which receive inputs from limbic structures such as the amygdala and hippocampus, respond to emotion-provoking or novel stimuli." The firing of some particular subset of Spiny I striatal neurons, then, will be triggered by some particular combination of environmental stimulation and patterns of movement. The excitatory loops (I and II) described above will ensure that this same subset will continue to fire for a period of time. Continuity of this pattern of activity is further assured by the interrelations between the Spiny I cells themselves. As illustrated in Figure 7, these are organised in the form of a lateral inhibitory network; thus, whichever subset of Spiny I cells is active at any one time, this subset will tend to inhibit firing in other such cells outside the set.

It remains to consider what might be represented by the particular set of cells that are active at a given moment in time. Basing their arguments on both the anatomical organisation of the basal ganglia as described above and the general theory of random associative networks (Rolls 1986a), Rolls and Williams (1987) have proposed an interesting answer to this question. Their proposal relates to the selection of an active subset of cells, not only in the striatum itself, but at all levels of the cortico-thalamo-striato-pallidal-midbrain circuitry depicted in Figures 5 and 6. We shall not go into the details of this proposal here. In brief, Rolls and Williams (1987) consider cells that, because of the particular chance patterns of connections they possess, receive inputs from both (1) neurons that respond to environmental cues associated with reinforcement (i.e., reward or the avoidance of punishment), and (2) other neurons that fire when the animal makes a movement that affects the occurrence of this reinforcement. They show how such cells might initially respond only to the conjunction of cue plus movement, but could eventually come to be activated by the cue alone, and so

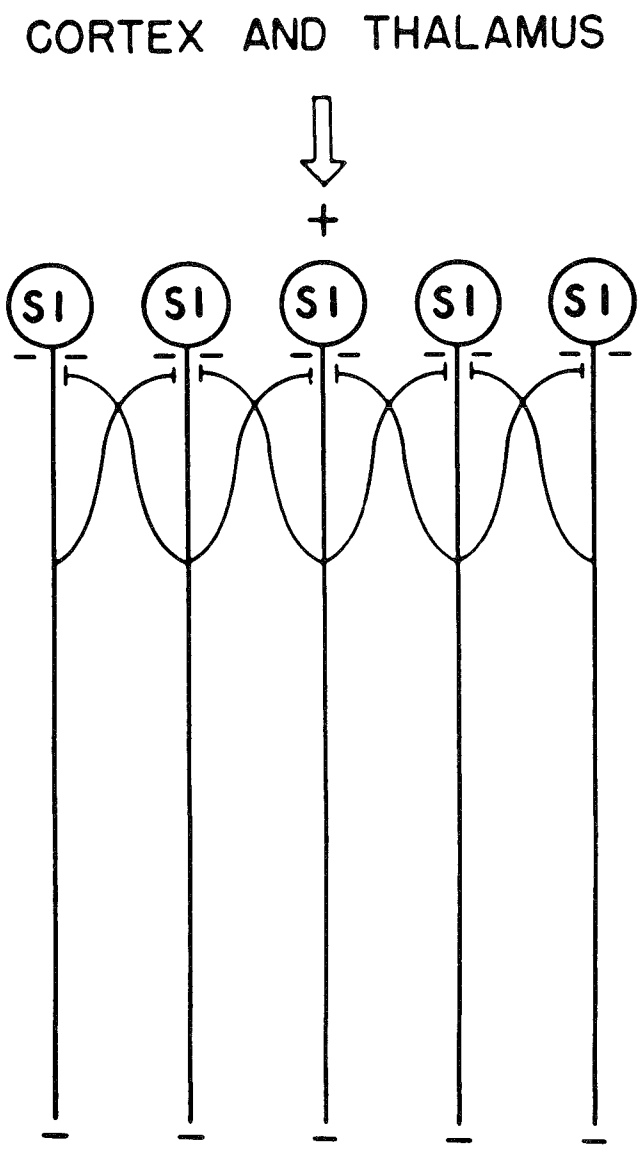

Figure 7. A schematic illustration of a small group of Spiny I neurons (SI) forming the lateral inhibitory Spiny I cell matrix, hypothesized to represent one functional cell system by which neostriatal efferent influence on voluntary movement is achieved. The synaptic interactions between Spiny I cells and their influence on targets are all inhibitory (−). From Groves (1983).

to participate in the production of the appropriate movement, given the cue. The particular set of neurons firing at a particular time in the basal ganglia, therefore, can be seen (a) as representing a step in a goal-directed motor program, and (b) as having been selected for this function by instrumental reinforcement mediated by the connectivity of the neurons that make up the set.

In the discussion so far we have distinguished between the caudate (Figure 5) and accumbens (Figure 6) motor systems anatomically but not yet functionally. In making this distinction we will concentrate on the functions of the accumbens system; the function of the caudate system has already been described adequately (for our present purpose) in the preceding paragraph (i.e., it encodes the specific content in terms of relationships among stimuli, responses, and reinforcement of successive steps in a goal-directed motor program). What, then, are the additional functions discharged by the accumbens system? Our answer to this question is twofold: (1) to switch between steps in the motor program; and (2) in interaction with the septohippocampal system, to monitor the smooth running of the motor program in terms of progress toward the intended goal.

We have supposed above that the firing of a particular subset of output neurons in the dorsal striatum and its associated neurons in other related structures (pallidal, thalamic, and so forth) represents a particular step in a motor program and that the firing of the set is maintained for a period of time by the positive feedback loops designated I and II in Figure 6. For a motor program conceived in this way to proceed as an integrated whole, there has to be an orderly transition from one step in the program to the next. The "orderliness" of such a transition can only be defined in terms of spatiotemporal progression towards the relevant reinforcer or "goal," i.e., the goal (a) which served initially to establish the motor program and (b) to which the program is currently directed. Thus, the "next" step must be the one that will most effectively bring the subject into greater spatiotemporal proximity to the relevant goal. How is this next step to be determined?

In the context of animal learning theory, the most common answers that have been given to this question depend on the concepts of the goal gradient and incentive motivation. The theories that use these concepts make the following basic assumptions. (1) Stimuli that do not initially have positively reinforcing properties come to acquire them as the result of Pavlovian conditioning in which they serve as CSs for an unconditioned positive reinforcer; the latter may be either a definite reward, such as food or water (providing the basis for approach behaviour), or the omission of an expected punishment (providing the basis for active avoidance). (2) The degree to which such CSs have positively reinforcing properties is a direct function of their proximity (in terms of time, space, or position in a series of chained stimulus-response links) to the initial UCS. (3) If the subject is simultaneously in the presence of more than one such stimulus, he directs his behaviour toward the one with the highest reinforcing power. These assumptions can, in principle, generate behaviour that maximises positive reinforcement (by approach to reward) and minimizes negative reinforcement (by active avoidance of punishment [Gray 1975]).

7. Limbic-striatal interactions

If we use these notions to help explain how the basal ganglia can ensure orderly transitions from one step to the next in their motor programs, we should look for a source of information about relations between environmental stimuli that are not innately reinforcing, on the one hand, and primary reinforcers, on the other. Rolls's group, using single-unit recording techniques in behaving monkeys, has provided considerable evidence for just such a source of information in the form of the input from the amygdala to n. accumbens; both these structures contain neurons that respond selectively to stimuli associated with reinforcement (Rolls & Williams 1987). It is hence plausible that this input is responsible for both determining the initial establishment of the sequence of steps that makes up a goal-directed motor program and guiding the orderly running of this sequence once its establishment is complete.

This is not all that is needed to ensure orderly transitions from one step to another in a motor program, however. In addition to the selection and initiation of the next step in the program (a function we have just attributed to the input from the amygdala to the nucleus accumbens), the termination of the step that is in progress must be considered. This would be expected to depend upon feedback indicating success in attaining the subgoal to which that step is directed (a subgoal presumably consisting of one of the secondary reinforcing stimuli initially established by way of the amygdalo-accumbens input). Given the assumption, developed in detail elsewhere (Gray 1982a), that the septohippocampal system performs just such a monitoring function (i.e., checking whether the actual and expected outcomes of motor programs match), it is natural to attribute the role of providing this feedback to the projection to n. accumbens from the subiculum. Furthermore, given the necessary correspondence between (1) the role of reinforcement in establishing an orderly sequence of motor steps and (2) the role of monitoring in determining that expected subgoals have been attained, we would expect a considerable degree of overlap in the projections from the subiculum and the amygdala, respectively, to n. accumbens. It is indeed known that these projections are both densest in the same caudomedial region of the nucleus accumbens (Phillipson & Griffith 1985), but information is not yet available about the interrelations between them at the ultrastructural level.

One more function is needed: The integration of these two processes (i.e., termination of the current step and selection of the next) requires quantization of time, over the whole set of interacting neurons, into units that correspond to the duration of a step in the motor program. This is an issue we touch on briefly later (see sect. 8, The model).

According to the model developed here, then, the relations between the basal ganglia, on the one hand, and the limbic system (i.e., hippocampus and amygdala) on the other, are central to the smooth establishment, running, and monitoring of motor programs. Now, motor programs are necessarily based (1) on expected relationships between responses and ensuing environmental events, these expectancies being built up by the process of instrumental conditioning; and (2) on expected relationships between

one environmental event and another, determined by the process of classical conditioning (Gray 1975). But there is evidence that the basal ganglia also play a key role in responding to the unexpected. As already noted, Rolls and Williams (1987) observed neurons in n. accumbens that respond to novel stimuli; they further report that such neurons show stable stimulus-specific habituation. These authors suggest that the inputs that determine these reactions by accumbens neurons to novel and familiar stimuli come from the hippocampus and/or amygdala, both of which also contain cells that respond selectively to novel stimuli. Other evidence for a role of the basal ganglia in reactions to novelty comes from studies of the behavioural effects of amphetamine and other dopamine-releasing drugs. These compounds elicit motor stereotypies and exploratory behaviour (forward locomotion, sniffing, and so forth); the former of these effects appears to depend on the release of dopamine in the caudate-putamen, the latter on dopamine release in n. accumbens (Iversen 1977; Kelly et al. 1975).

Further light is cast on the role of the basal ganglia in responding to novelty (or, more generally, their role in attention) by considering two efferent pathways that connect these structures to the mesencephalon, as illustrated in Figures 8 and 9. Figure 8 shows the output of the accumbens system to the pedunculopontine nucleus, part of the mesencephalic motor region (Yang & Mogenson 1987); this structure appears to be part of the pathway by which dopamine released in n. accumbens increases exploratory locomotion, sniffing, and so forth (Kelly et al. 1975). Figure 9 shows an important output from the caudate system to the superior colliculus (Williams & Faull 1988), a structure known to be of importance in the control of head movements, eye movements, and visual attention (Dean & Redgrave 1984; Wurtz & Albano 1980). Note that this, as well as other outputs from the caudate, is also potentially under the control of neurons in n. accumbens, because accumbens Spiny I GABAergic efferents include among their targets the dopaminergic cells of the substantia nigra which, in turn, innervate the caudate-putamen (Somogyi et al. 1981).

If limbic-striatal interactions are important for both

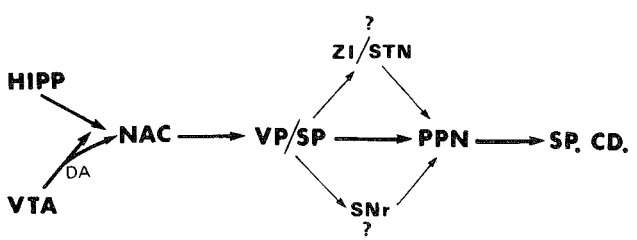

Figure 8. Model proposed by Yang & Mogenson (1987a) for the routes by which hippocampal and accumbens output signals are transmitted to motor effector sites to elicit locomotor activity. The heavier arrows are the major pathways investigated by Yang and Mogenson; the lighter arrows are suggested alternative pathways. HIPP, hippocampus; VTA(DA), ventral tegmental area dopaminergic neurons; NAC, nucleus accumbens; VP/SP, ventral pallidal and subpallidal area; ZI/STN, zona incerta, subthalamic nucleus; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus, part of the mesencephalic locomotor region; SP CD, spinal cord. From Yang & Mogenson (1987a).

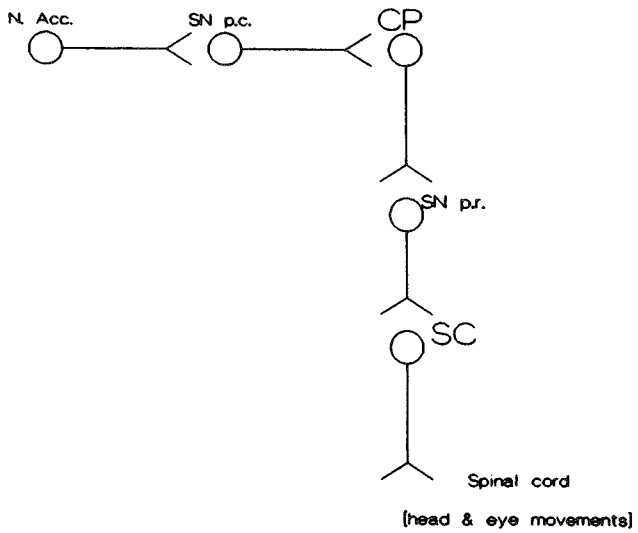

Figure 9. Connections from nucleus accumbens to caudate-putamen and thence to the superior colliculus. N. Acc., nucleus accumbens; SN p.c., substantia nigra, pars compacta; CP, caudate-putamen; SN p.r., substantia nigra, pars reticulata; SC, superior colliculus. Based on data in Somogyi et al. (1981) and Williams & Faull (1988).

motor programming and the organisation of responses to novelty, as the foregoing arguments suggest, what happens when the demands of these two functions conflict? Behaviourally, the answer to this question is clear: Reactions to novelty take precedence. Indeed, a major component of the behavioural reaction to novel stimuli (if these are sufficiently powerful; see the discussion of Zuckerman 1982, in Gray 1982b) consists in inhibition of all ongoing motor programs (Gray 1975; 1982a). [See also Zuckerman: "Sensation Seeking: A Comparative Approach to a Human Trait" *BBS* 7 (3) 1984.] This function has been attributed elsewhere to the septohippocampal system (Gray 1982a), and indeed specifically to the output from the subiculum to n. accumbens (see preface to Gray 1987), a postulate that is congruent with the proposal by Rolls and Williams (1987) that accumbens neurons that respond selectively to novelty do so in virtue of the inputs they receive from the hippocampus (see above). If, however, the novel stimulus is of little biological significance (i.e., is neither itself a reinforcer nor signals any change in existing contingencies of reinforcement), and if it is repeatedly presented to the animal, then the specific behavioural reactions it initially elicits rapidly diminish and disappear (habituation), allowing a resumption of whatever motor programs are appropriate to the given environment.

This process of habituation may also be considered within the context of motor programming. Two cases may be envisaged. In the first case, the initially novel stimulus occurs at random with respect to the ongoing motor program; in this case, for smooth running of the program, it is only necessary to ensure that the initial reactions to the one-time novel stimulus are suppressed. In the second case, the initially novel stimulus bears a reliable relationship to some step or other in the ongoing motor program; in this case, expectation of the one-time novel stimulus will be built into the motor program, with the

consequence that the initial reaction it elicits is replaced by one that is appropriate to the program. Furthermore, if the one-time novel stimulus is integrated into a motor program in this manner, it would be expected to continue to receive attention (whereas, in the first case, attention to the stimulus will be diminished or lost). This type of attention will differ, however, from the reflex attention elicited by an unexpected stimulus: The temporo-spatial locus of the stimulus and its perceptual features will be expected (i.e., predicted as part of the motor program) and their occurrence will be monitored accordingly. (It is an interesting possibility that the difference between these two kinds of attention – to novel and expected stimuli – corresponds to the distinction between controlled and automatic processing considered earlier in this article; we return to this possibility later.)

In the necessity for these interactions between the behavioural responses and cognitive processing involved in reactions to novelty and their habituation, on the one hand, and motor programming, on the other, we begin to see a rationale for having one set of brain structures to discharge both these apparently distinct functions. It is therefore reasonable to suppose that each of the different kinds of behavioural change in the reaction to an initially novel stimulus distinguished above is accompanied, and may even be produced, by a corresponding change in the subicular input to n. accumbens.

A role in the final process described above (i.e., the change from reflex to programmed attention) also appears to be played by the prefrontal cortex, however. The frontal eye fields as well as other prefrontal cortical areas project directly to both the superior colliculus (Leichnetz et al. 1981) and oculomotor centres in the brainstem (Leichnetz 1981). Seagraves and Goldberg (1987), studying conscious monkeys under a variety of behavioural conditions, recorded from neurons in the frontal eye fields with demonstrated projections to the superior colliculus and concluded that some of these cells fire in relation to purposive saccades, i.e., saccades made to a target whose occurrence is predicted on the basis of prior learning. A disturbance in the normal functioning of this prefrontal projection to the superior colliculus may provide a plausible neural basis for the well-documented schizophrenic deficit in smooth pursuit eye movements (Holzman 1987; Iacono 1988; Levin 1983; 1984; Lynch 1987), though the specificity of this deficit to schizophrenia is still under debate (see Levin et al. 1981). Such an account would find support in the observation that binding of the glutamate receptor ligand, kainic acid, is elevated in the frontal eye fields in schizophrenic brains (Nishikawa et al. 1983). If both the subiculum and the prefrontal cortex are involved in this type of programmed attention, the activities of the two regions could be coordinated by way of n. accumbens or the cingulate or entorhinal cortices.

8. The model

The major components of our model have now been presented; in this section we try to put them to work. We begin by reviewing the main assumptions, each discussed above, on which the model is based. In considering the implications of these assumptions, Figure 10 may be

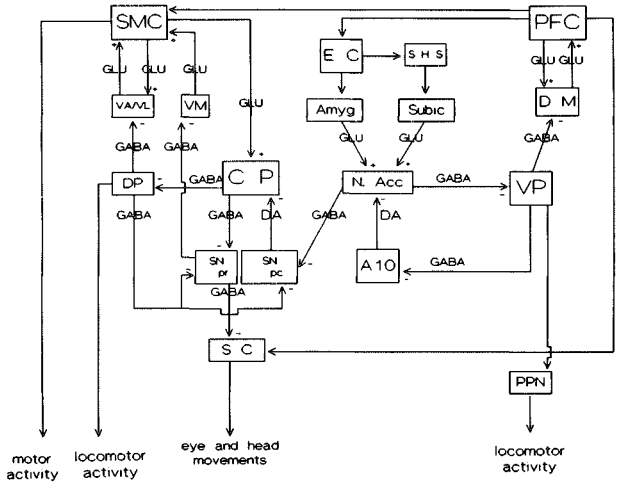

Figure 10. Interrelations between the basal ganglia and the limbic system. Structures: SMC = Sensorimotor cortex; PFC = Prefrontal cortex; EC = Entorhinal cortex; SHS = Septohippocampal system; Subic = Subicular area; Amyg = Amygdala; VA/VL = N. ventralis anterior and ventralis lateralis thalami; VM = N. ventralis medialis thalami; DM = N. dorsalis medialis thalami; DP = Dorsal pallidum; VP = Ventral pallidum; CP = Caudate-putamen; N.Acc = N. accumbens; SNpr = Substantia nigra, pars reticulata; SNpc = Substantia nigra, pars compacta; A10 = N. A10 in ventral tegmental area; SC = Superior colliculus; PPN = Penduculopontine nucleus. Transmitters: GLU = Glutamate; DA = Dopamine; GABA = γ-aminobutyric acid.

helpful; it illustrates the various building blocks of the model, as well as the interrelations among them.

1. The caudate system (Figure 5), by way of its connections with sensory and motor cortices, encodes the specific content of each step in a motor program (e.g., for a rat, turn left at a junction in a maze; or, for a human being, the next word to be spoken in a sentence).

2. The accumbens system (Figure 6) operates in tandem with the caudate system so as to permit switching from one step to the next in a motor program.

3. Both the establishment of the sequence of steps that makes up a given motor program and the subsequent orderly running of the program are guided by the projection to n. accumbens from the amygdala; this projection conveys information concerning cue-reinforcement associations.

4. The septohippocampal system (Figure 4) is responsible for checking whether the actual outcome of a particular motor step matches the expected outcome; this information is transmitted to n. accumbens by the projection from the subiculum.

5. The activities of the caudate, accumbens, and septohippocampal systems are coordinated and kept in step with one another by the prefrontal cortex, acting by way of its interconnections, respectively, with (i) the cortical components of the caudate system (Figure 5) and the superior colliculus (Leichnetz et al. 1981; Seagraves & Goldberg 1987); (ii) n. accumbens, dorsomedial thalamus (Figure 6) and amygdala; and (iii) the entorhinal and cingulate cortices (Figure 4).

6. The maintenance of the pattern of activity in a subset of striatal, thalamic, and cortical neurons that makes up a motor step results from the reverberatory excitatory activity in Loops I and II, together with lateral

inhibition (Figure 7) in the striatum. These patterns of activity are periodically interrupted by the firing of the dopaminergic inputs to the striatum at the termination of Loop III.

7. The duration of a step in a motor program corresponds to the joint operation, in both the caudate and accumbens systems, of Loops I-III (Figures 5 and 6).

8. Timing is coordinated between the septohippocampal monitoring system and the basal ganglia motor programming system. Given assumptions 6 and 7 above, and given the assumption that time is quantized in the septohippocampal system by the theta rhythm (Gray 1982a), corresponding to an instant of about a tenth of a second, this must also be the duration of a motor step. (There are various possible routes by which coordination between the septal pacemaker cells for the theta rhythm and, e.g., the dopaminergic cells of A10 might be assured, but these will not be discussed here.)

9. As well as participating in motor programming, both the caudate and accumbens systems play important roles in organising behavioural responses to novelty (Figures 8 and 9) and controlling the interactions between such responses and motor programming; this function is under the control of the subicular input to n. accumbens.

Armed with these assumptions, let us consider what might happen during the running and monitoring of a particular motor program. We start with the moment at which activity in a particular subset of neurons (striatal, thalamic, and cortical), corresponding to a particular step in a motor program, is interrupted by the arrival of an inhibitory dopaminergic input to the striatal Spiny I cells, completing Loop III. A dopaminergic input of this kind should be an automatic consequence of the architecture of the feedback loops that make up the circuits depicted in Figures 5 and 6; and it should take place (simultaneously, we suppose) in both the dorsal and the ventral striatum. A further consequence of this input will be disruption of the lateral inhibition (Figure 7) exercised by the currently active set of Spiny I neurons. This combination of dopaminergic inhibition and the disruption of lateral inhibition provides an opportunity for striatal activity to be switched into a new pattern. The topographical specificity of the dopaminergic innervation of the striatum, however, is insufficient on its own to determine the selection of such a new pattern of activity. Indeed, without further change in other striatal inputs, the most likely outcome would be a resumption of the same pattern of activity that has just been interrupted (as this must previously have been selected because of the strength of its relevant inputs). Thus the arrival of the dopaminergic input to the striatum is best seen as providing a temporal window permitting change, rather than as providing a direction to that change.

Where are we to find the topographical specificity that would permit the selection of a new pattern of striatal activity then? By way of reply, we make use of a proposal of Jacques Glowinski's (Glowinski et al. 1984) outlined earlier in this article. There is evidence that glutamate enhances dopamine release from terminals in both the dorsal striatum and n. accumbens, and that dopamine in turn inhibits glutamate release (Cheramy et al. 1986; Chesselet 1984; Marien et al. 1983; Romo et al. 1986). Glowinski points out that the combination of these two effects provides a mechanism by which the point-to-point glutamatergic afferents to the basal ganglia (such as those from the subiculum) could activate a specific set among the otherwise widely ramifying dopaminergic afferents to the same regions, thus localising dopaminergic inhibition to a particular set of synapses. In particular, then, we propose that, supplementing the global dopaminergic inhibition that occurs at the termination of Loop III in both dorsal and ventral striatum, there is local release of dopamine in n. accumbens activated by the glutamatergic afferents from the subiculum. For this proposal to do the theoretical work we require of it, the particular configuration of synapses activated in this way at any given time must result in extra inhibition of those Spiny I cells in n. accumbens that have just been firing. In this way, the subicular input to n. accumbens would be responsible for terminating the motor step that has just been completed. Given the monitoring function we attribute to the septohippocampal system, such an input from the subiculum would correspond to the message, *match*, that is, the actual outcome of the just-completed motor step and the expected outcome coincide.

We turn now to the selection and initiation of the next step in the motor program. The assumptions set out above make it clear that this must be the responsibility of the amygdalar input to n. accumbens; this input encodes information about cue-reinforcement associations (Rolls 1986b). We accordingly suppose that the amygdalo-accumbens projection will activate a new set of accumbens Spiny I cells corresponding to that motor step that maximally increases spatiotemporal proximity to the goal of the current motor program. Activation of this set of accumbens cells will in turn activate corresponding sets of cells in the dorsomedial thalamus and then in the prefrontal cortex (Figure 6). The newly activated cells in the prefrontal cortex will accordingly alter the inputs to the sensorimotor cortex and thence to the caudate system (Figure 5), eventuating in the specific motor content that corresponds to the set of accumbens Spiny I cells initially picked out by the amygdalar reinforcement signal. At the same time, the prefrontal cortex will access another corresponding set of cells in the septohippocampal system (via the entorhinal and/or cingulate cortices; see Gray 1982a), allowing the new motor step to be monitored as before.

Consider next what happens if an ongoing motor program is interrupted by the occurrence of an unexpected event (or by the failure of an expected event to occur). Given the assumptions outlined above (see Gray 1982a), this must result in (1) inhibition of the motor program and (2) exploratory behaviour directed to the novel event.

With regard to the first of these, Gray (1987, p. vii) suggested that the capacity for normal behavioural inhibition may depend on the subicular projection to n. accumbens, as this provides a route by which activity in the septohippocampal system is able directly to affect motor behaviour. There are now several experiments whose results run counter to this proposal, however. Jarrard et al. (1986) showed that cytotoxic lesions of the hippocampus proper, including the dentate gyrus, produces disinhibition (seen as increased resistance to extinction after training on a continuous reinforcement schedule in the alley), even though the subicular area was left undamaged; extending the lesion to include the subiculum did not add to this effect (although it did reduce resistance

to extinction after training on a partial reinforcement schedule). Similarly, surgical section aimed at disconnecting the subiculo-accumbens pathway did not increase resistance to extinction after continuously reinforced training but it did reduce resistance to extinction after partially reinforced training (Rawlins et al. 1989). Subicular damage thus seems to leave the capacity to inhibit motor programs intact. These findings do not resolve the issue, however, of what component(s) of the septohippocampal system and its projections mediate inhibition of motor programs (see Gray 1982, p. 278, for some possibilities). We have some evidence suggesting that fibres running in the descending columns of the fornix may make a significant contribution (Rawlins et al. 1989).

With regard to the second behavioural consequence of exposure to novelty – exploratory behaviour directed toward the novel event – these same experiments do implicate the subiculo-accumbens pathway, because both subicular lesions (Jarrard et al. 1986) and section of this pathway (Rawlins et al. 1989) impair the normal tendency to learn to ignore the novel event of nonreward embedded in a partial reinforcement schedule. It may therefore be proposed that the detection of novelty is communicated from the septohippocampal system to n. accumbens via this route, activating the downstream output from the latter structure to the pedunculopontine nucleus (Yang & Mogenson 1987a; see Figure 8), giving rise to exploratory behavior, coordinated with visual search by way of the pathway, via the dorsal striatum, to the superior colliculus (Figure 9). This hypothesis is consistent with Yang & Mogenson's (1987a) observations of increased exploratory behavior elicited by chemical activation of subicular afferents to n. accumbens.

We must finally ask what happens if the initially novel event occurs repeatedly in a way that allows it to be incorporated into (i.e., predicted as an expected consequence of) the motor program. Under these circumstances, we suppose, the sensory features of the once-novel event come to be predicted by the septohippocampal comparator system (Gray 1982a), with the consequence that the subicular input to n. accumbens becomes increasingly restricted topographically, until it again corresponds to a match message. To the extent that the once-novel event requires modification in the motor program (e.g., by appropriate detection of its now-expected occurrence), this would occur by way of changes in the particular steps encoded by the interacting prefrontal cortex, caudate, accumbens, and superior collicular systems. This hypothesis is consistent with our observations that the partial reinforcement extinction effect (i.e., habituation to the repeated nonreward embedded in a partial reinforcement schedule, giving rise to increased resistance to extinction when the animal is tested with only repeated nonreward) is weakened by subicular damage (Jarrard et al. 1986) and eliminated by section of the subiculo-accumbens pathway (Rawlins et al. 1989).

There is a possible analogy between the sequence of events activated by repeated exposure to an initially novel event that we have just ascribed to the functioning of the subiculo-accumbens pathway and the passage from controlled to automatic processing proposed in some theories of human cognition. According to Schneider and Schiffrin (1977), automatic processing comes to occur as the result of prolonged practice on a task; it is then considered to require no processing capacity, to occur outside conscious awareness, and to involve direct access to long-term memory of past regularities. If taken seriously, the analogy suggests that an intact subiculo-accumbens pathway is necessary to mediate the transition from controlled to automatic processing and perhaps also that the direct access to long-term memory that characterises automatic processing is mediated by the interconnections between the septohippocampal system and the memory stores of the temporal lobe (Gray 1982a). Taking the analogy one step further, our proposal that schizophrenia arises partly because of disturbed functioning of the subiculo-accumbens pathway is isomorphic to the hypothesis (e.g., Frith 1979, p. 233) that the disease arises from a disruption in automatic processing. As a consequence, cognitive activity "must proceed at the level of consciously controlled sequential processing" (Venables 1984, p. 75). The analogy is clearly speculative, but it may have heuristic value.

9. Applications of the model

Given this model of the interactions between the striatal motor programming system and the septohippocampal monitoring system, we next consider the predictions it makes for the consequences of two interventions relevant to the analysis of schizophrenia developed above: the administration of amphetamine (or other dopamine-releasing, psychotomimetic drugs) and damage to the subiculo-accumbens projection (which, as we have seen, is likely to be impaired in schizophrenia).

The administration of amphetamine will cause increased release of dopamine throughout the basal ganglia, inhibiting Spiny I cells indiscriminately and thus overcoming the topographical specificity we have attributed to the action of the subicular input to the accumbens. This process would be expected to disrupt the running of all steps in all motor programs indiscriminately, thus leaving the motor output of the striatal systems to be determined in other ways. At this point we see two possibilities. First, one motor step, or a short series of motor steps, may develop a dominance over all others and occur repetitively in consequence of continued reverberatory activity in Loops I and II; this would give rise to the stereotyped motor behaviour seen in amphetamine-treated animals. Second, behavior may be controlled by those outputs of the basal ganglia that are concerned with reactions to novelty (as after a massive subicular input to n. accumbens; see above), giving rise to exploratory behaviour and exaggerated attention to (relatively) novel stimuli. Empirically, it appears that motor stereotypy occurs particularly when excessive dopaminergic activity is most marked in the dorsal striatum and that exploratory behavior occurs when it is most marked in n. accumbens (Iversen 1977; Kelly et al. 1975). Stereotypy is mediated by the projection from the striatum, via the substantia nigra, to the superior colliculus (Figure 9; Pope et al. 1980), whereas locomotor exploration is mediated by the output from the accumbens to the pedunculopontine nucleus (Figure 8; Yang & Mogenson 1987).

Essentially the same predictions apply to the destruc-

tion or weakening of the subiculo-accumbens projection. Loss of the subicular input to n. accumbens will again disrupt the smooth running of motor programs, with the consequence that behavioural control will revert to novel stimuli, or that familiar stimuli will be treated (because of the absence of a match message from the subicular comparator) as though they were novel. These developments may be reinforced if there is either increased dopaminergic activity (as observed after hippocampal lesions by Mitchell et al., unpublished) or up-regulation of dopamine receptors consequent upon reduced dopaminergic activity (as reported after the same lesions by Springer & Isaacson [1982]) in n. accumbens, because such changes are likely to be indiscriminate with respect to the orderly running of motor programs. There is one important way the predictions for an impaired subiculo-accumbens projection differ, however, from those for dopamine-releasing drugs: Interruption of the subiculo-accumbens projection will not directly affect the caudate system, and should not therefore result in motor stereotypy. A second important difference concerns the way the effects of the two interventions should be altered by dopamine-receptor blocking (neuroleptic) drugs. The effects of an indirect dopamine agonist, such as amphetamine, should be largely reversible by these compounds. The effects of interruption of the subiculo-accumbens projection, in contrast, should be reversible only to the extent that they are due to the resulting putative changes in dopaminergic function; moreover, however extensive these may be, there are likely to be other consequences of damage to this projection. Because our hypothesis attributes schizophrenia in part to damage of this kind, data on the behavioural effects of neuroleptics after section of the subiculo-accumbens projection would be of particular value; none are yet available.

This model of the interactions between the striatal and septohippocampal systems, applied to the cognitive abnormalities of acute schizophrenia, can be seen to treat these as a special kind of disorder in motor programming and monitoring. Disorders of motor activity have long been reported in clinical studies of schizophrenia (Kraepelin 1919), and have recently been re-emphasised by Owens et al. (1982). On the model presented here, such disorders should be closely related to the cognitive abnormalities of schizophrenia. This is a possibility that has received little experimental attention; but at least one study has demonstrated a good correlation between a measure of formal thought disorder in schizophrenia (the type-token ratio as applied to speech) and disturbances in "the orderly expression of skilled movements" (Manschreck et al. 1981). At a more theoretical level, the model can be brought into relatively direct contact with both Hemsley's (1982; 1987a) and Frith's (1987) descriptions of the underlying psychological deficit in schizophrenia. As noted above, Hemsley's proposal is that schizophrenia arises from a weakening of the effect of previous experience on the selection of environmental stimuli to which to attend and respond (i.e., a weakening in Broadbent's [1977] mechanism of "pigeon-holing"). It is just such an effect of previous experience on motor programming (interpreted broadly to include the programming of selective attention as well) that is attributed in our model to the subiculo-accumbens projection; and it is just this projection that, we suggest, is impaired in schizophrenia. Similarly, Frith's proposal (Figure 1) is that "willed intentions are not monitored correctly" in schizophrenia. The equivalent of "willed intentions" in our terminology is the running of a motor program by the interacting prefrontal cortex, amygdala, caudate and accumbens systems; and the monitoring of such willed intentions must accordingly fall to the projection from the subiculum to n. accumbens. On this analysis, then, schizophrenia could again be attributed to a disruption in the subiculo-accumbens projection.

Frith and Done (1988) make the related suggestion that (as proposed by Gray 1982a) information about intended motor programs is provided to the septohippocampal monitoring system via the projections from prefrontal cortex to the entorhinal and cingulate cortices and that one can therefore consider schizophrenia to result from disruption in these projections. This hypothesis is not inconsistent with our own: The pathology observed postmortem in the schizophrenic hippocampal formation and parahippocampal gyrus may indicate impaired input from prefrontal to entorhinal cortex, impaired output from subiculum to n. accumbens, or both. (Given assumption 3 above, it is clear that our model predicts in general terms that disruption of the normal functioning of the amygdalar input to n. accumbens would also have severe consequences for the running and monitoring of motor programs; we have not yet worked out this aspect of the model in any detail, however.)

Another relevant model, related to both Frith & Done's (1988) views and the present arguments, is that of Weinberger (1987). He sees the primary neurological basis of schizophrenia as lying in an *underactive* dopaminergic (mesocortical) innervation of the dorsolateral prefrontal cortex. This is thought to lead – as demonstrated in the rat after 6-OHDA-induced lesions of prefrontal dopaminergic terminals by Pycock et al. (1980) and illustrated in Figure 11 – to increased (mesolimbic) dopaminergic input to striatal regions. This model has the virtue that it accounts for the evidence (reviewed by Weinberger 1987) of impaired functional activity in the schizophrenic prefrontal cortex; this could be secondary, as observed in monkeys by Brozowski et al. (1979), to

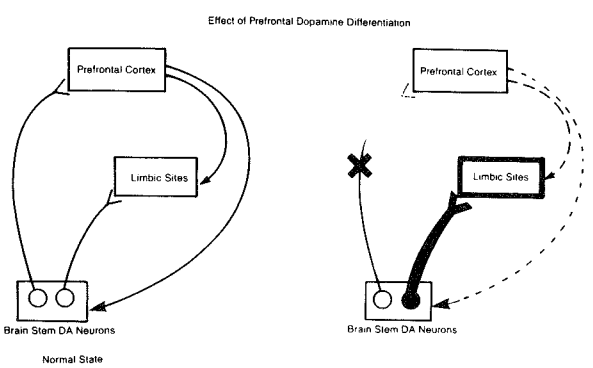

Figure 11. Schematized interactions between mesolimbic and mesocortical dopamine systems in normal state (left) and after selective lesioning of dopamine input to prefrontal cortex (right), based on the work of Pycock et al. (1980). Broken line indicates that specific effect of lesion on corticolimbic feedback (e.g., decreased inhibition or increased excitation) is unknown. DA indicates dopamine. (From Weinberger 1987)

impaired dopaminergic input to this region. At the same time, Weinberger's model explains the well-known evidence for dopaminergic overactivity (attributed now exclusively to the mesolimbic system) in schizophrenia, as well as the link between the two types of pathology (frontal underactivity and dopaminergic overactivity). A possible isomorphism between this model and both Frith & Done's (1988) and the present ones will be apparent from a consideration of the anatomical routes that might underlie the arrow in Figure 11 from "prefrontal cortex" to "limbic sites." One such route would go via the projection from prefrontal cortex to entorhinal and cingulate cortices (emphasised by Frith & Done), followed by the projection from the latter structures to the hippocampal formation and thence to n. accumbens, as emphasised here.

It would be otiose at this stage to speculate which of the possible interruptions in these circuits, if any, is primary. More detailed pathological observations on the schizophrenic brain will be needed first. Nor do we wish to speculate about the etiology of the dysfunction that affects these circuits in the schizophrenic brain (an issue that is well discussed by Murray et al. [1988] and Weinberger [1987]). Rather, our primary intention has been to show how such a dysfunction can be related to the cognitive abnormalities that characterise the positive symptoms of acute schizophrenia. In so doing, we have concentrated on the interaction between the dopaminergic and subicular inputs to n. accumbens. This relatively narrow focus has heuristic advantages, both for the design of experiments and in rendering more concrete the theoretical issues involved. It would be astonishing, however, if the cognitive abnormalities of acute schizophrenia were always to reflect precisely the same neurological dysfunction, and even more astonishing if the limited data now available had allowed us to identify this with any accuracy. We hope, nonetheless, that the arguments developed above will have indicated some fruitful lines for further theoretical and experimental development.

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A faulty negative feedback control underlies the schizophrenic syndrome?

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Gray et al. have presented a reasonable psychological and neurophysiological background to their model, emphasizing the defective integrative capacity of the schizophrenic brain. They focus on the balance between two antagonistic pathways converging on the spines of the spiny I GABAergic neurons of the nucleus accumbens, i.e., the presumably glutamatergic neurons derived from the subiculum and the dopaminergic neurons from A10. They rightly describe this aspect of their model as a special case of an interaction which has previously been proposed in more general terms (Carlsson 1988). They take a different path, however, in their further elaboration: whereas our model is based on a negative cortico-striato-pallido-thalamo-cortical feedback loop, the corresponding loop II of their model, shown in Figs. 5 and 6, is a positive feedback loop. This raises some difficulties in understanding the role of the mesostriatal dopaminergic pathway which, they agree, should be looked upon as antagonistic to the corticostriatal glutamatergic pathway. Since the positive feedback loop is proposed to enhance mental and motor activities and the dopaminergic system modulates this function in an antagonistic sense, dopamine should be an inhibitor of mental and motor activities, which is obviously in disagreement with established facts. Penney and Young (1986) have previously presented a similar model with the same inherent problem (for references and comments, see Carlsson 1988).

In our model, loop II, which incidentally needs further investigation to clarify its more detailed circuitry (see Carlsson & Carlsson 1990), is proposed to serve as a negative feedback loop, which is thus inhibitory on mental and motor activities. The antagonistic modulator dopamine then facilitates mental and motor functions, which is in agreement with available evidence. According to Gray et al. the function of dopamine would be to interrupt the reverberating activity of their loops I and II, thus permitting a switch from one pattern of activity to another. In the absence of dopamine one and the same pattern of activity would accordingly be expected to go on continuously. In reality, however, the absence of dopamine brings about an almost complete loss of motor and mental activity. This suggests that loop II, in the absence of the dopaminergic antagonistic influence, is capable of blocking psychomotor activity very efficiently. In support of this contention, the administration of glutamatergic antagonists, acting either noncompetitively or competitively on the glutamatergic NMDA receptor, has been found to induce motility in dopamine-depleted mice (Carlsson & Carlsson 1989a; 1989b; Carlsson & Svensson 1990; and unpublished observations).

The ability to switch from one pattern of activity to another is certainly important. However, we know of no evidence that this capacity resides in the dopaminergic system. Rather, our observations support the view that the glutamatergic system plays an important role in this function. After NMDA blocking receptor in dopamine-depleted mice the animals start to move again, but apparently they are unable to switch from one activity to another. Their activity is largely restricted to forward locomotion. Thus the glutamatergic system appears to serve at least two functions in this context, namely, to inhibit psychomotor activity and, by releasing the inhibition selectively, to choose the activity pattern deemed to be adequate in a given situation. In support of this contention, experiments in monoamine-depleted mice show that motility can be induced by combined treatment with a muscarinic receptor antagonist and the alpha-2-receptor agonist, clonidine. In this case, where the glutamatergic system was intact, the animals showed a more normal behavior, with preserved ability to switch between different behavioral patterns. Needless to say, however, the selection of an appropriate behavioral pattern must depend on complex circuitries, presumably involving both cortical and subcortical structures.

An important aspect to consider is the possible influence of feedback loops on the handling of sensory information being relayed to the cortex by the thalamus. We have proposed that an important function of the cortico-striato-pallido-thalamic pathway is to restrict the information relayed to the cortex in a selective manner, giving priority to novel and significant stim-

uli. Because the dopaminergic system is inhibitory on this pathway, increased dopaminergic activity would allow more information to reach the cortex. In addition, the existence of collaterals of the pallido-thalamic pathway projecting to the mesencephalic reticular formation will lead to an influence on the cortical arousal. Excessive dopaminergic activity will thus not only overload the cortex with sensory input, it will also cause hyperarousal, resulting in mania or psychosis, depending on the degree of integrative capacity of the cerebral cortex.

Gray et al. cite evidence that glutamate can enhance transmitter release from dopaminergic nerve terminals, whereas dopamine can inhibit transmitter release from glutamatergic nerve terminals in the striatum. This issue is further complicated by preliminary observations of Imperato et al. (1990), indicating an apparently differential action of glutamate on dopamine release, where the stimulation of glutamatergic non-NMDA receptors enhances dopamine release and stimulation of NMDA receptors has the opposite effect. NMDA-receptor antagonists accordingly enhance the release of dopamine. The possibility may thus be considered that different parts of the heterogeneous striatal tissue are differentially influenced by the glutamatergic system. Moreover, the glutamatergic and dopaminergic systems appear to interact at an additional level. We have observed that in monoamine-depleted mice NMDA-receptor antagonists increase the responsiveness of dopaminergic receptors to the mixed D-1, D-2 receptor agonist apomorphine and to the D-1 receptor agonist SKF 38393. Even more striking is the enhanced response of alpha-2-adrenergic receptors to clonidine following treatment of monoamine-depleted mice or rats with NMDA-receptor antagonists (Carlsson & Carlsson 1989c; Carlsson & Svensson 1990).

Don't leave the "psyche" out of neuropsychology

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Few current observers of schizophrenia would wish to challenge the idea that our knowledge of the disorder can be increased by examining and theorising about the brain. Currently there are two ways, profoundly different ones philosophically, to construe this line of inquiry. According to organic psychiatry, it as a "search for the lesion." Alternatively, it as an attempt to extend our understanding of the neurophysiological correlates of normal mental experience and behaviour and of the aberrations to which they are prey.

What is interesting about the model proposed by Gray and his colleagues is that it spans both of these perspectives. Although it wisely avoids speculation about the "aetiology of the dysfunction," the model clearly expects an eventual neurological explanation of schizophrenia. On the other hand, the general form of the theory is very much in the tradition of the "conceptual nervous system" models developed in normal individual-difference research by Eysenck (1967), Zuckerman (1984), and others – including, of course, Gray (1982a) himself. As such, it ought to be attractive to those, like ourselves, who are more committed to a dimensional view of schizophrenia rather than seeing it as a neurological disease. For us, however, the theory's inability to capture the essential quality of psychosis makes it seem less promising.

The main reason for our doubt is that the model places a heavy explanatory burden on relatively low-level brain structures and brain circuitry, marginalising the possible influence of the higher nervous system as the *primary* physiological vehicle for schizophrenia. We appreciate that such an emphasis is necessary to sustain the argument for animal modelling. Here the authors adopt a familiar logic: Even though the aberration of consciousness – reflected in thought and language – that is central to schizophrenia is characteristically human, a simpler "marker" for this, and one that is functionally responsible for it, can be identified and investigated across species. The argument is identical to one used some years ago by one of the present authors (Claridge 1978) when presenting the case that LSD-25 is more valid ecologically than amphetamine as a potential drug model of schizophrenia. (Incidentally, Gray et al. are invited to comment further on this comparison, which lack of space precludes us from restating in detail here.) The problem, however, is to find a marker behaviour that can be transferred to animals but is neither so nonspecific nor so low-level (even in humans) that it fails to bridge the gap to what seems peculiar to schizophrenia.

The above dilemma is illustrated in Gray et al.'s choice, in this respect, of latent inhibition. A perfectly convincing explanation of latent inhibition is that it merely represents a form of habituation (Mackintosh 1983). If interpreted in this way the phenomenon loses much of its specificity and uniqueness as a marker for schizophrenia. Anomalies of orienting and habituation have been studied for years by psychophysiologists seeking a microcosm of cognitive disorder in schizophrenia, usually in similarly low-level conceptual nervous system models of functions (Dawson & Nuechterlein 1984; Gruzelier & Venables 1972; Spohn & Patterson 1979; Venables 1973). Gray et al. make no reference to this huge body of research, which also failed in its purpose. Perhaps it really is time to admit that schizophrenia is a uniquely human condition. After all, unlike with such "simpler" mood-based psychopathologies as anxiety, no one has ever demonstrated a convincing example of schizophrenia in an animal, either naturally occurring or experimentally induced.

This does not exclude some continuity of process with lower animals – and hence the lower brain – but it does suggest that the latter may not be the primary site of dysfunction in schizophrenia. Two related sets of observations are relevant. One concerns evolutionary aspects of the genetics of schizophrenia (Crow 1990; Karlsson 1978). The other concerns the interpretation of cognitive disturbance in schizophrenia as a dysfunction of hemisphere organisation (e.g., Posner et al. 1988; Walker & McGuire 1982), particularly when these are related to developmental aspects of the disorder (Birchwood et al. 1988). Notably, too, in a recent unpublished study (Claridge et al., submitted) we demonstrated a clearly lateralised influence on – and theoretically predictable gender difference in – the "negative priming" effect, an information processing paradigm relevant to schizophrenia which Gray et al. themselves cite as support for their comparative theory.

One last point, in case it should seem that we have underestimated or misunderstood the tentative role Gray et al. assign to the higher nervous system in schizophrenia. They draw freely on neuropathological, including postmortem, data about the "schizophrenic brain." Quite apart from the almost embarrassing *variety* of data here (Jackson 1990), the methodological flaws in their collection must surely be evident: small samples, lack of base-rate information, poor controls, incidental influences in life, difficulties of retrospective diagnosis, continuing controversies about whether schizophrenia is a unitary condition, and other deficiencies which would draw the wrath of colleagues toward any clinical psychologist claiming to have discovered a discriminating feature of schizophrenia! Until the basic "psychometric" properties of such observations have been established, it is surely premature to build such an elaborate bottom-up theoretical structure on top of them.

The limbic-striatal interaction: A seesaw rather than a tandem

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We agree with Gray et al. that some sort of impaired subiculo-accumbens projection may underlie psychological and motor deficits in schizophrenia (cf. Ellenbroek & Cools 1990). Gray et al.'s hypothesis is based on the assumptions summarized in section 9. Some of these are directly supported by hard evidence: For example, the amygdala-accumbens projection has been found to be necessary for facilitating the mechanisms by which conditioned, or secondary, reinforcers come to control behaviour (Cador et al. 1989; Everitt et al. 1989). Other assumptions, however, are difficult to reconcile with data collected recently in our laboratory. Still, incorporating these data into Gray et al.'s model does not invalidate it, but rather extends its predictions concerning the neurological basis of schizophrenia.

As discussed by Gray et al. (Assumption 2), both the "accumbens" system and the caudate ("striatal") system are known to permit the organism to switch from one step to the next in programming all action plans, including those involved in the cognitive sphere (Cools 1980; Oades 1985; Robbins & Everitt 1982). Today, however, there is evidence that each system has its own subtle role in this process of switching. It has long been known that the striatal system allows the organism to switch arbitrarily to non cue-directed behaviours – be they cognitive or motor – (Cools 1980; for review: Cools 1990). Recently, we have found evidence that the accumbens system allows the organism to switch to cue-directed behaviours (van den Bos & Cools 1989; for review: Cools 1990). In this context it must be noted that cues are defined as external stimuli, originally neutral (irrelevant) ones that are singled out in advance. Recent experiments in our laboratory have also shown that an active accumbens system is accompanied by an inactive striatal system, whereas an inactive accumbens system is accompanied by an active striatal system (Cools et al. 1990). Moreover, it has been found that an organism with a deficient striatal system is fully dependent on its accumbens system, and vice versa (for review: Cools 1990). In other words, the two systems are not operating in tandem (Assumptions 2 and 7) but like a seesaw. From this point of view it is evident that the consequences of a dysfunctioning accumbens system – because of an impaired subiculo-accumbens projection, for instance – can also be seen in organisms with a dysfunctioning striatal system. These findings accordingly add a new dimension to the model: It may not be just an impaired subiculo-accumbens projection that underlies the psychological and motor deficits in schizophrenia but also impairments of the striatal system.

Finally, we feel that the discussion of the role of the basal ganglia in responding to novelty needs some elaboration (assumption 9). Recently, we have provided evidence in favour of the hypothesis that challenges – be they environmental or pharmacological – enhance the release of noradrenaline in the accumbens with the consequence that the neural input of the subiculo-accumbens projection is inhibited: Only the neural activity of the amygdala-accumbens projection gets access to the accumbens (Cools et al., in press). Coping with, or habituation to, such challenges is accompanied by a decrease in the noradrenergic activity in the accumbens with the consequence that the neural input of the amygdala-accumbens projection is inhibited: Only the neural input of the subiculo-accumbens projection gets access to the accumbens (Cools et al., in press). According to Gray et al.'s model, these data imply that challenges weaken the influence of stored regularities of previous input on current perceptions (viz., the consequence of a suppressed subiculo-accumbens input: cf. Hemsley 1987a): The organism is now able to facilitate the mechanisms by which secondary reinforcers are coupled to primary reinforcers to control behaviour (viz., the consequence of an undisturbed amygdala-accumbens input: see Cador et al. 1989; Everitt et al. 1989).

Given that an enhanced noradrenaline content is found to occur in the accumbens of schizophrenic patients in several post-mortem studies (Bird et al. 1980; Farley et al. 1978; Kleinman 1987), the above-mentioned data predict that these patients have at least suffered from (a) a reduced ability to use stored memories of regularities of previous input on current perceptions (a consequence of a suppressed subiculo-accumbens input), and (b) a strengthening of the coupling of irrelevant stimuli to primary reinforcers (a consequence of an open amygdala-accumbens input). Since an accumbens marked by a closed hippocampal gate and an open amygdaloid gate disrupts the seesaw between the "accumbens" and "striatal" systems such that the striatal system is relatively hyperactive (cf. Cools et al., in press; Cools 1990), one can predict that such patients have also suffered from an enhanced ability to switch ongoing behaviour arbitrarily (see above).

In sum, we agree with Gray et al. that the disruption of normal functioning in the subiculum, basolateral amygdala, nucleus accumbens, or their corresponding afferents and efferents may underlie psychological and motor deficits in schizophrenia, in particular Type I. In addition, we feel that the "striatal" system too is important in this respect.

Given this insight, we feel that there is an urgent need to stop considering schizophrenia as a single entity, but as a cluster of subentities, each having its own characteristic neural, cognitive, and motor deficits. For this reason, it is necessary to concentrate on subtle differences resulting from deficits in the distinct parts of the circuitry under discussion rather than to focus on a single part of the circuitry.

As a final remark, we have used Gray's terminology insofar as it concerns the "striatal" and "accumbens" systems. To be precise, we prefer to define the striatal system as those parts of the striatum which are innervated by A9 dopaminergic neurons projecting to the dorsal pallidum as well as the substantia nigra, pars reticulata, namely, the dorsal striatum. We prefer to define the accumbens system as those parts of the striatum that are innervated by A8 and A10 dopaminergic neurons projecting to the ventral pallidum as well as the substantia nigra, pars compacta, namely, the ventral striatum.

Motor disturbances in schizophrenia

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In this impressive neuropsychological synthesis, Gray and his associates propose that at least some of the cognitive symptoms of schizophrenia can be attributed to a failure in the monitoring of motor programs. The proposed mechanism of the monitoring failure is a disruption of the subicular input to nucleus accumbens. I believe the authors' emphasis on output dysfunction to be a salutary return to a once prominent but currently neglected theme in the psychopathology of schizophrenia. In particular, the Gray et al. proposal prompts a reconsideration of the diagnostic and theoretical importance of motor abnormalities in schizophrenia.

Classical accounts of schizophrenia are replete with discussions of such motor disturbances as choreoathetoid movements, grimacing, mannerisms, impulsive acts, negativism, stereotypies, and perseverations (Bleuler 1950; Kraepelin 1971). Motor disturbances are much less frequently attended to and reported on in current clinical practice, and there is general

agreement that dramatic motor symptoms are rare (Manschreck 1986). Nevertheless, careful observation and testing reveals a high frequency of more subtle forms of motor disturbance (Manschreck 1986; Owens et al. 1982). For example, Manschreck et al. (1982) observed some form of spontaneous or elicited motor disturbance in virtually every case of conservatively diagnosed schizophrenia, as opposed to a 25% incidence in a control group of manic, schizoaffective, and severely depressed patients. Some form of spontaneous motor disturbance was observed in fully 67% of the schizophrenic patients and only 7% of the controls. Significantly, Manschreck et al. found a substantial relationship between the degree of motor disturbance and the degree of formal thought disorder in the schizophrenic group. Yarden and Discipio (1971) likewise observed severe thought disorder in 78% of schizophrenic patients with motor disturbance as opposed to 17% of patients free of such disturbance.

Of the schizophrenic motor disturbances, stereotypy and perseveration have been particularly prominent in clinical and research commentaries. Stereotypy is the regular and uniform repetition of apparently purposeless motor activity, including both simple and complex forms. Perseveration refers to the repetitive intrusion into succeeding contexts of a response appropriate to a preceding context. Stereotypy is most likely to be observed in patients' spontaneous behavior, whereas perseveration is most likely to be prompted by the serial nature of psychological testing or experimental tasks (e.g., Freeman & Gathercole 1966). Perhaps because of these differing observational settings, stereotypy and perseveration are usually considered distinct phenomena. Yet they share the characteristics of iteration and decontextualization, as well as an autonomous, autochthonous quality. These similarities may point to a common mechanism.

Bleuler (1950) described at length spontaneous schizophrenic stereotypies of movement, speech, writing, and cognition. He was obviously intrigued by "the tendency toward stereotypy" (p. 27), which he regarded as "of paramount importance for the understanding of schizophrenia" (p. 458). Although Bleuler recognized that stereotypy was not specific (fundamental) to schizophrenia, he nevertheless regarded the tendency toward stereotypy as a primary expression of the underlying disease process. Shakow (1963; 1977) was similarly impressed by the evidence of perseveration in his experimental studies of schizophrenia. For Shakow, the schizophrenic patient lacks historicity and so fails to evaluate properly the relative familiarity or novelty of events: "he reacts to old situations as if they were new ones (he fails to habituate) and to new situations as if they were recently past ones (he perseverates)" (Shakow 1963, p. 303).

The prominence of stereotypy and perseveration in schizophrenic behavior is matched by a viable animal model of stereotypy and by tentative efforts toward a model of perseveration. Little needs to be said of the value of stimulant-induced stereotypy as a model for exploring the neurochemical mechanisms and pathophysiology of schizophrenia (e.g., Segal & Janowsky 1978; Lieberman et al. 1990). Less has been accomplished in developing an animal model of perseveration. However, I have elsewhere suggested (Crider et al. 1986) that disrupted latent inhibition or blocking may be considered forms of attentional perseveration. In both paradigms the animal first attends to and then fails to ignore a novel stimulus that normally produces habituation. As noted by Gray et al., Solomon and I showed that both chronic amphetamine administration and neuroleptic-induced supersensitivity of the dopamine receptor disrupt latent inhibition (Solomon et al. 1981) and blocking (Crider et al. 1982; 1986). In addition, we showed that both forms of attentional perseveration can be reversed with dopamine receptor blockers. Other animal models of dopamine-mediated perseveration have also been explored (Evenden & Robbins 1983; Ridley & Baker 1983).

Gray et al. suggest that both amphetamine-induced stereotypy and amphetamine-induced disruption of latent inhibition and blocking are due to a dopamine-mediated failure of the subiculo-accumbens monitor (sect. 10, para. 2). Assuming that dopamine-mediated disruption of latent inhibition and blocking reflects a perseverative process, Gray et al. thus provide the common mechanism for stereotypy and preservation in animals implied by the descriptive similarity of the two phenomena. Hence stereotypy and perseveration in schizophrenia are also plausibly secondary to a failure of the subiculo-accumbens monitor, although the causes of this failure remain to be isolated.

In sum, the concept of a subiculo-accumbens monitoring failure, which Gray et al. use primarily to account for the positive cognitive symptoms of schizophrenia, can as readily be used to account for schizophrenic stereotypy, perseveration, and perhaps other motor disturbances. As Gray et al. note (sect. 10, para. 4), their model implies a relationship between motor disturbance and cognitive dysfunction in schizophrenia. This implication is consistent with available evidence (Manschreck 1986; Yarden & Discipio 1971). To put the matter somewhat more pointedly, motor signs may be as valid as cognitive symptoms in defining the psychotic state in schizophrenia. This conclusion finds surprisingly little echo in either current diagnostic practice or in experimental studies. Gray et al. give us ample justification for rethinking our contemporary neglect of the motor manifestations of schizophrenia.

The neuropsychology of schizophrenia: A perspective from neurobehavioral genetics

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Gray et al. have presented an admirable integration of an enormous amount of both clinical and experimental data (deriving from many different fields: neurology, psychiatry, neuroanatomy, neurochemistry, etc.) to arrive at the most complete hypothesis about the neural bases of schizophrenia to date. According to their model, most disruptions of the complex neural pathways involved will lead to schizophrenic symptoms. Both genetic and environmental influences may, separately or together, have multiple effects at many different places in these neural systems. Hence one of the strengths of the present model is that it provides a way to explain schizophrenia's well-known heterogeneity with regard to symptomatology (e.g., Dworkin et al. 1988; Van Eerdewegh et al. 1987) and presence or absence of certain biological markers in defined subgroups of patients (e.g., Markianos et al. 1990), but also with regard to the genetic correlates underlying this psychiatric disease (e.g., Baron 1986; Faraone & Tsuang 1985; Kennedy et al. 1988).

I disagree with the authors, however, where they state, in the final paragraph of the target article, their belief that it would be futile, at least at this stage, to speculate about which of the many possible interruptions in the neural circuits they have described is primary. Of course, because schizophrenia seems to be more like a heterogeneous set of disorders than a well-defined syndrome, there just might not exist a single primary interruption. Others, however, have argued in favor of a unitary concept of schizophrenia (e.g., Heath et al. 1989). If that were true, then there might indeed exist only one single primary interruption. Damage to the hippocampal system is a good candidate for this primary lesion that leads ultimately to schizophrenia. This hypothesis is supported by several findings, of which I mention two.

First, it has been observed that pregnancy or birth complications (PBCs) increase a person's risk of developing schizo-

phrenia (Mednick 1974). These PBCs include anoxia, prolonged labor, multiple births, and so on. Cerebral ischemia is known to lead to the release of glutamate in the hippocampus, which has an excitotoxic action that may be reinforced by the simultaneous release of zinc (Tønder et al. 1990), resulting in neuronal cell loss in the hippocampus. Second, serum obtained from schizophrenic patients has recently been shown to contain an antibody, a subfraction of gamma G immunoglobulin, which is reactive against an antigen occurring primarily in the septal region of the brain (Heath et al. 1989).

These findings suggest a number of possible causes for schizophrenia (PBCs; immunological disorder, possibly induced by viral action), but all acting via the same or almost the same primary lesion to the septohippocampal system. Similar considerations have led Schmajuk (1987) to propose that hippocampally lesioned animals might constitute an animal model of schizophrenia. Since hereditary factors might predispose certain individuals to susceptibility to environmentally induced neural damage, I suggest that an even more appropriate model may be found when different inbred strains are compared for their susceptibility to anoxia. Also, not all schizophrenic patients have experienced PBCs and schizophrenia shows familial aggregation (see Gottesmann & Shields 1982), suggesting that purely hereditary factors may sometimes be the sole cause of schizophrenia. Large heritable differences in hippocampal anatomy can be found between different inbred mouse strains (Crusio et al. 1986), particularly with regard to the sizes of their infra- and intrapyramidal mossy fiber (IIP-MF) terminal fields. Note that the hippocampal mossy fibers, being the axons of dentate granule cells that form synapses on the dendrites of hippocampal pyramidal cells in area CA3, constitute a bottleneck in the flow of information into the hippocampus (cf. Fig. 4, where the mossy fiber projection is indicated by the word "Gate"). It might therefore be worthwhile to investigate the possibility that certain inbred strains provide a genetic model of schizophrenia. From experiments carried out in our laboratory, it would appear that strains such as DBA/2, NZB/B1N, or CPB-K are likely candidates. These have only small projections of the zinc-containing IIP-MF (Crusio et al. 1987) and exhibit a number of features that are characteristic for hippocampally lesioned animals, such as poor learning in spatial radial-maze tasks (Crusio et al. 1987; Schwegler et al. 1990) combined with good performance in two-way active-avoidance tasks (Lipp & Schwegler 1983). We may speculate that these mice suffer a hereditary malfunction of their septohippocampal system, a notion supported by psychopharmacogenetic evidence (van Abeelen 1989). An interesting question is whether these mice also exhibit other neurological features that are found in schizophrenic patients.

The foregoing speculation about the possibility that the primary origin of schizophrenia is damage to the septohippocampal system need not contradict the observed heterogeneity of the schizophrenic syndrome. It might well be that in combination with the initial septohippocampal damage, whatever its origin, multiple genetic and environmental effects exert modulating influences on some of the different components of the neural circuits described by Gray et al. and thereby cause the heterogeneous appearance of the schizophrenic syndrome. I suggest that multivariate genetic studies, simultaneously investigating psychiatric and neurological variables (selected according to Gray et al.'s model) combined with studies along the lines proposed by Vogel and Motulsky (1986, p. 607), will provide clues to unravel the complex etiology of schizophrenia.

Heterogeneity, orienting and habituation in schizophrenia

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Gray et al. cite three behavioral phenomena in support of their neuropsychological model, particularly in support of the notion that acute schizophrenic patients are unable to integrate memories of past regularities with current perceptions and motor programs: latent inhibition, the Kamin blocking effect, and the partial reinforcement extinction effect. This commentary points out that (1) results from other behavioral phenomena that rely on memories of past regularities are more problematic for the model and (2) the key psychological process in the three behavioral phenomena cited by Gray et al. may not be the integration of past memories with current perceptions.

(1) Other behavioral phenomena that rely on the use of memories of past regularities have produced results which do not appear to be entirely consistent with the proposed model. One such phenomenon is the elicitation and habituation of the orienting response. The orienting response is associated with attention to novel, unexpected, or significant stimuli and was originally referred to by Pavlov (1927) as an "investigatory response" or "what is it?" response. Habituation of the orienting response as a function of repetition of the eliciting stimulus is an example of memory of past regularities guiding current perceptions and behavior. For acute schizophrenia, the Gray et al. model predicts greater than normal orienting ("over-attention") and also slower than normal habituation because of the inability to integrate memories of past regularities of stimulus exposures with current perceptions.

What do the orienting and habituation results obtained with acute schizophrenic patients show then? The most commonly used measure of the orienting response with schizophrenic patients is the skin conductance response, which is a momentary increase in the electrical conductivity of the skin associated with sympathetic nervous system activation. A remarkably consistent finding across laboratories is that a large subgroup of schizophrenic patients (usually between 40% and 50%) fail to exhibit any skin conductance orienting response to novel innocuous stimuli (Bernstein et al. 1982; Dawson & Nuechterlein 1984; Holzman 1987; Öhman 1981). Among the patients who do respond, the most commonly reported abnormality is fast habituation, although some investigators also have reported subgroups which are slow to habituate. These findings have been observed, although not necessarily to the same degree, in both acute and chronic schizophrenics and in both patients receiving neuroleptic drugs and those not receiving them (Bernstein et al. 1982). Thus, the heterogeneity in the elicitation and habituation of the orienting response among acute schizophrenics does not appear consistent with the Gray et al. model.

Individual differences in the skin conductance responding among schizophrenic patients have been associated with different attentional dysfunctions. Dawson (1990), for example, stated that "the responders may be deficient in the ability to inhibit the allocation of attentional resources to irrelevant environmental stimuli – the nonresponders, on the other hand, may be deficient in the ability to actively allocate attentional resources to environmental stimuli . . . " (1990, p. 249). The skin conductance responder is therefore hypothesized to show "over-attention," which is consistent with the Gray et al. model, whereas the nonresponder is expected to show "under-attention," which is inconsistent with the proposed model. Also, individual differences in the skin conductance orienting response have been related to differences in brain glucose metabolism. Preliminary evidence indicates that nonresponder unmedicated schizophrenic patients are lower than both responder patients and matched normal controls in glucose

metabolism assessed by PET in the medial and lateral frontal cortex, and in the hippocampus (Dawson 1990, Hazlett et al., submitted). The relationship between reduced hippocampal activity and reduced orienting appears contrary to the Gray et al. hypothesis that reduced hippocampal activity should be associated with increased dopamine activity in the nucleus accumbens and therefore with "over-attention." Whether or not this relationship is contrary to that predicted by the Gray et al. hypothesis, the main point remains that the finding of heterogeneity, which is a hallmark of schizophrenia data, must be incorporated into any complete theory of schizophrenia.

(2) If large subgroups of schizophrenic patients do not orient and habituate in a way that suggests the weakening of the influence of memories on current perceptions, then why do they apparently perform poorly on the behavioral paradigms cited by Gray et al.? To answer this question, we need to identify processes which distinguish orienting and habituation from the three behavioral phenomena discussed by Gray et al. One process that these three have in common with each other, but not with the typical orienting and habituation paradigm, is that they involve the ability to detect and respond flexibly to the *change* in the meaning of the past regularities. Thus, for example, latent inhibition requires subjects to detect a change in the predictive value of a stimulus. Likewise, in the Kamin blocking effect, subjects must recognize that a formerly redundant noninformative stimulus is now informative. The partial reinforcement extinction effect also involves learning that a response that was partially reinforced previously is now never reinforced. Thus, unlike the orienting and habituation paradigms, the three behavioral phenomena share the fact that the rules change in the middle of the game; that is, they are reversal learning tasks. However, the fact that acute schizophrenic patients fail to show these behavioral effects implies the implausible: that patients are *better* able to detect changes in stimulus contingencies than both controls and chronic schizophrenics. This appears to be inconsistent with other findings in schizophrenia; for example, acute schizophrenics have been shown to perform poorly on the Wisconsin Card Sorting Test, which challenges the ability to change a conceptual set in response to changed reinforcement contingencies (Kolb & Whishaw 1983).

Another difference between orienting and habituation and the three behavioral phenomena is that the latter are tested in a context of a task which requires discrimination between relevant and irrelevant events. In contrast, in the typical orienting and habituation paradigm, only one stimulus is presented repeatedly and no task is required. In support of the importance of this difference, Öhman et al. (1986) tested schizophrenic patients in a modified orienting and habituation paradigm that involved presentation of relevant and distracting stimuli. Öhman et al. found that the patients oriented less than normal to task-relevant stimuli, but more than normal to the distracting stimuli. This observation suggests that in certain attentional activating tasks a subgroup at least of schizophrenic patients continues to process irrelevant stimuli whereas controls show habituation. This provides a plausible and context specific basis for exhibiting less than normal latent inhibition, Kamin blocking, and partial reinforcement extinction.

In conclusion, the orienting and habituation findings do not support the Gray et al. model, suggesting that the critical psychological deficit is not simply a weakening of the influences of past memories of regularities on current perceptions. Other processes have been suggested which could be incorporated into the model and further explored in this context. We congratulate the authors for providing a model with the ability to integrate psychological, neurological, and pharmacological levels of analysis. They have given us a glimpse of what a truly integrative theory of schizophrenia must aspire eventually to be.

How does the physiology change with symptom exacerbation and remission in schizophrenia?

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In search of the biological basis of psychotic symptoms, Gray et al. propose a deficit in excitatory subicular output to the nucleus accumbens. This promises to become a directly testable hypothesis – if it is not one already. Although Gray et al. associate this deficit with positive symptoms of schizophrenia, they do not consider in detail the possible relationship between such a deficit and the large changes in positive symptoms that occur during the exacerbation and remission of psychosis in schizophrenia. We review current clinical studies and current thinking on the biology of these changes, then discuss the connection with the proposed deficit of Gray et al.

The waxing and waning of active psychosis in schizophrenia, and its relation to dopaminergic neurotransmission, remains a continuing puzzle. Positron emission tomography (PET) with neuroleptic tracer has demonstrated that responders and nonresponders to neuroleptic treatments have similar levels of dopamine receptor occupancy (Wolkin et al. 1989). Thus, some other factor beyond dopamine receptor blockade is clearly responsible for the persistence or nonpersistence of the psychotic state. A similar PET study after drug withdrawal has found that most neuroleptic drug molecules are dissociated from dopamine receptors after 5 days (Smith et al. 1988). Not all patients relapse in the second week after neuroleptic withdrawal, however. Rather, they show times-to-relapse (on placebo) described by a broad exponential density function (Davis et al. 1980; Hogarty & Ulrich 1977). Remission on drug or relapse off drug usually occurs, albeit delayed or incomplete, *on a timetable separate from either the establishment or the loss of dopamine blockade.* The "other factor" or factors involved may be assumed to require the permissive effect of altered dopamine transmission.

Such a factor also seems to *result in* changes of dopamine metabolism. Initially with neuroleptic treatment, the feedback pathways from the striatum and perhaps other dopamine projection areas to the midbrain cause increased firing of dopamine cells there, as if in an effort to overcome the neuroleptic blockade. The attendant increased turnover of dopamine later appears to diminish in responders, however, because levels of homovanillic acid (HVA; the major dopamine metabolite exiting brain) in plasma decrease with symptomatic improvement after several weeks of drug treatment and rise with worsening after drug withdrawal (Davila et al. 1988; Pickar et al. 1986).

What brain mechanism could fulfill the role of such an "other factor," perhaps able to influence behavior and one or more brain dopamine systems? Delayed adjustments within the dopamine system in response to chronic drug exposure are possible and have been proposed. The "depolarization block" phenomenon is a prime candidate (Grace & Bunney 1986). After the early feedback increase in dopamine cell firing with neuroleptic treatment, the feedback excitation effect apparently becomes excessive with chronic treatment and drives these cells into a state of continuous depolarization, with attendant paralysis of dopamine release. Unfortunately, this candidate mechanism from the animal literature does not fit all the data, since withdrawal of neuroleptic produces a sudden resurgence of dopaminergic transmission as the paralysis is lifted (Grace & Bunney 1986), whereas, as noted above, only a few patients relapse suddenly upon drug withdrawal.

The catecholaminergic "stimulant abuse" model offers another explanation relevant to this commentary. The explanation is limited to statements on conditioning mechanisms, as the

neurobiology of these is not entirely clear. The emergence of paranoid psychotic features with the chronic use of amphetamines has often been described as indistinguishable from paranoid schizophrenia (Snyder 1973). These psychotic symptoms, according to the model, emerge gradually from more normal arousal and investigatory behaviors activated by the drug, as some of these are selectively enhanced by simultaneously active catecholamine reinforcement pathways (Ellinwood et al. 1977). In chronic amphetamine abuse, the drug instigates the dual arousal and reinforcement actions, whereas in schizophrenia, endogenous dopamine and norepinephrine dysregulation may be responsible. Work with the experimentally induced amphetamine psychosis has revealed classical conditioning: environmental cues chronically paired with amphetamine administration later produced arousal by themselves. Operant conditioning also occurred, with the emergence of stereotyped behavior sequences incorporating some behaviors which had occurred coincidentally with earlier drug administration (Ellinwood et al. 1977). In keeping with this model, an explanation for the reduction of both plasma HVA and psychotic behavior with chronic neuroleptic treatment is the extinction of otherwise self-reinforcing elevated dopamine neurotransmission "behavior." Similarly, drug-free relapse could develop some time after both catecholaminergic arousal and catecholaminergic reinforcement return. Stress may influence relapse through its ability to increase brain catecholamine activity.

To anyone trying to understand the physiology of remission and relapse, the repeated testing of patients for latent inhibition during acute exacerbation and remission (described in sect. 4, para. 15) is of particular interest. The study cited (Baruch et al. 1988) reports that the patients studied longitudinally all improved, so the issue of return of latent inhibition in drug-treated nonresponders could not be addressed, and the exact cause of the change (direct drug effect or clinical improvement) was not determined. There are other, biological, measures closely tied to the cognitive events felt defective by Frith and Done and by Hemsley (sect. 2) and to related processes (sect. 8) – the so-called "endogenous" event-related potentials (ERPs). [See also Verleger: "Event-related Potentials and Cognition" 11 (3) 1988.] These potentials have been widely studied in schizophrenia, and one, the "late positive complex" or "P300," has been studied longitudinally. The late positive complex indexes the evaluation of stimuli for novelty and task relevance. It has low amplitude in schizophrenia, and this finding is highly correlated with state change, not medication effect (Duncan et al. 1987; Levit et al. 1973; Steinhauer & Zubin 1982). Low P300 amplitude also correlates with positive symptom severity across individuals (Shenton et al. 1989). ERPs associated with self-initiated movements correspond especially to attentional involvement in movement preparation (bereitschaftspotential or BP) and perhaps the receipt of movement feedback (reafferent potential or P2). Both have been reported abnormal in schizophrenia – low amplitude for the BP (Chiarenza et al. 1985; Kaku et al. 1986) and delay or absence of the P2 (Timsit-Berthier et al. 1973; Takasaka 1985) – but these have not yet been studied longitudinally.

The crucial question here regarding Gray's hypothesis is: What exactly changes with symptom exacerbation and remission? Does hippocampal output to accumbens change, secondarily affecting dopamine release? Or are changes in dopamine transmission itself responsible for all the fluctuations, uncovering a static hippocampal outflow deficit, which is then covered up by neuroleptic blockade? Further longitudinal studies of patients across the different states of their illness, with a range of physiologic measures, may allow us to refine this important hypothesis of Gray et al.

Dopaminergic excess or dysregulation?

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Gray et al. have provided an important and testable model of schizophrenia that relates the impairment in attentional and executive functions to impaired interaction between the septohippocampal system and the ventral striatum. The phenomenological feature that appears most specific for schizophrenia is the proposed inability to monitor internally produced action programs, as suggested by Frith. This is a very interesting model, but one cannot be sure of the evidence for an important involvement of the subiculum in this activity. It is not clear that unilateral or bilateral hippocampectomy produces psychosis (or alien cognitive control phenomenon) and one would expect the model to predict this.

A major criticism is the assumption that the dopamine excess model of schizophrenia is valid. The animal studies reported in the target article depend on this assumption. This model is based on studies of dopaminergic drug effects on an idealized synapse, coupled with an understanding of the clinical effects of these agents. The "synaptosomal soup" preparation is a poor model of mental function for several reasons. It tells us about acute effects of medications on single synapses that are artificially isolated from the effects of anatomical connections that ordinarily modulate neuronal activity. The brain does not consist of isolated synapses and the clinical drug effects we are most interested in do not occur immediately. Dopaminergic projections in general have a high degree of reciprocal regulation. This is true not only for the mesocortical and mesolimbic projections, but also for projections to right and left caudate, amygdala and ventral striatum, septum and ventral striatum, and septum and medial frontal cortex (Louilot et al. 1985; 1988; Simon et al. 1988). Dopaminergic modulation may be enhanced in some projections and (given the reciprocal regulation) reduced in others. Perhaps the most appropriate question is which projections have increased release and which have inhibited release of dopamine.

We have previously observed increased blood flow in the left globus pallidus of neuroleptic-naive schizophrenic patients. We have interpreted this finding as evidence for reduced dopaminergic modulation of the left ventral striatum (Early et al. 1989a; 1989b). This interpretation is supported by demonstrations of right-sided hemineglect (Bracha 1987; Posner et al. 1988), some of which are eliminated (Bracha) or reversed (Tomer 1989) by antipsychotic treatment. Reports of increased dopamine receptor number in the left striatum (Farde et al. 1990) would be compatible with a dopaminergic denervation of this structure.

This perspective leads to a question of whether hippocampal lesions produce an increase or a decrease in dopamine utilization in the ipsilateral ventral striatum? Springer and Isaccson's (1982) results indicate a decrease in dopamine utilization followed by a compensatory increase in receptor number. The neurochemical evidence cited for this is supported by a number of behavioral studies supporting this conclusion (Isaacson 1984). Gray's model postulates disrupted communication between ventral subiculum and ventral striatum, with the alterations in dopaminergic release as a secondary effect. Decreased, increased, or no dopaminergic modulation of the ventral striatum would presumably be compatible with this model.

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A focalized deficit within an elegant system

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Gray et al. have made a commendable attempt to integrate a broad spectrum of data and theory in a model intended to solve the riddle of schizophrenia. Building such a model is like decorating an imaginary Christmas tree. The tree is the theoretical model, the ornaments are empirical findings. One must be mindful that the ornaments are valid. Equally important, if the final outcome is askew, one must remember that it is the tree that needs to be altered, not the ornaments.

The neuroanatomical specificity of Gray et al.'s model and the considerable amount of animal research supporting it leads to many testable predictions for schizophrenia. Previous neuropsychological theories of schizophrenia have focused on more global hemispheric differences accounting for schizophrenic deficits (e.g., Cromwell 1987; Gruzelier 1984; Venables 1984); it is encouraging to see Gray and others leading a trend towards neurological explanations of increasing specificity and sophistication. It seems strange, however, that the extensive body of laterality research is not even mentioned by the authors, as it represents the bulk of neuropsychological research that has actually been conducted with schizophrenics. It also seems a bit premature, though parsimonious, to attribute the two schizophrenic psychological deficits separately proposed by Hemsley (1987a) and Frith (1987) to disruptions in a single (subiculo-accumbens) projections (sect. 10, para. 4), a rather specific anatomical locus for such complex functions.

The authors work with the hazard of using animal data and models to help explain schizophrenia. They note that while animal models were previously viewed as inappropriate, recent data concerning underlying cognitive deficits in schizophrenia allow such models to be applied (sect. 1, para. 3). This is fine if the fundamental deficits of schizophrenia are the same as those reported from animal work. Are the sequencing of words in a sentence (syntax) in humans and the sequencing of motor programs in a rat truly analogous functions, however, attributable to the same neural network (as implied by the authors in sect. 9, para. 1)? For an animal model to be applied definitively to schizophrenia, it would be gratifying if the model (a) designated which structures and functions (in kind or degree) are present in people but not in animals, and if it (b) asserted that these uniquely human properties were in no way involved in the pathology of schizophrenia. Until this is done, the application of animal models and data remains a hazardous but admirable adventure.

Gray et al. have chosen to focus their model on neurological and cognitive hypotheses which account primarily for the positive symptoms of schizophrenia, and perhaps this is regrettable. Historically, positive symptoms gained prominence in schizophrenia not because of their primacy, but because they were more amenable to operational definition (American Psychiatric Association 1980). Bleuler (1950) described hallucinations and delusions as "accessory" symptoms and viewed disturbances of affect, association, ambivalence, and autism as "basic." That is, the latter are more stably present, whereas the accessory symptoms come and go. Only limited features of these "basic" symptoms could be defined as positive. By consequence, Gray et al. are confronted with this question: Are they possibly dealing with phenomena peripheral rather than central to schizophrenia?

In addition, the authors relate findings of temporal lobe pathology to dopaminergic hyperactivity (sect. 6, para. 5 and sect. 10, para. 3) without explaining why structural damage to the temporal lobe in general (or subiculo-accumbens projection in particular) does not result in the continuous presence of positive symptoms. Although periodic dopaminergic hyperactivity could account for the episodic nature of positive symptoms, the disappearance of these symptoms during periods of remission does not seem congruent with morphological abnormalities and neuronal loss in the temporal lobes of schizophrenics, conditions one would expect to remain relatively constant.

An alternate and possibly more fruitful strategy might be to investigate the neurological basis of schizophrenia-related variants (SRVs; Cromwell 1984), which are present not only during acute illness but also (a) premorbidly, (b) in remission, and (c) in healthy first-degree relatives. These SRVs, which include measures of attention and information processing, represent more stable characteristics of schizophrenia and possibly more appropriate phenotypes for genetic investigations than the clinical symptoms of the disorder.

Although Gray et al. prefer to skirt issues of etiology, in the future their model should not leave out the genetics of schizophrenia. Since the model explains a broad array of schizophrenic symptoms with a specific, localized deficit, a mono- or oligogenic model of inheritance is suggested. However, the authors should be mindful that the impressive bulk of genetic findings in schizophrenia is compatible with a polygenic explanation (Gottesman & Shields 1982). The latter view would seem more difficult to reconcile with Gray et al.'s hypothesis of deficit within a specific neuroanatomical structure.

Gray and his colleagues were a bit selective, if not circumscriptive, in choosing to focus their model on two relatively recent formulations of cognitive deficit (Frith 1987; Hemsley 1987a). Of the two, Hemsley's hypothesis that schizophrenia involves "a weakening of the influences of stored memories of regularities of previous input on current perception" (sect. 2) appears to have greater credibility, both clinically and experimentally. Clinically, parents and relatives often report the surprise and pain of having the patient, after years of loving relationship, respond to them with no affect or even with paranoid retaliation (e.g., Willick 1990). Empirically, Hemsley's formulation seems to fit the model more directly as based upon the latent inhibition, Kamin blocking, and partial reinforcement extinction effects (PREE). Frith's hypothesis, that a breakdown occurs in the monitoring of "willed intention," does not seem to fit as well. Moreover, it would appear to disagree with observations that the behavior of schizophrenics is overdetermined by the immediately prior stimuli from which they fail to disattend or disengage (Cromwell & Dokecki 1968; Posner et al. 1988; Salzinger 1971). In other words, a monitoring problem does indeed exist, but it may apply to stimulus intention as well as willed intention.

Although the cognitive views of Hemsley and Frith are dealt with seriously, earlier views of the nature of schizophrenic deficits are not handled so well, at least in this initial presentation. For example, Shakow (1963) viewed the fundamental problem in schizophrenia as the failure to maintain a mental set (readiness to respond) beyond a limited period of time. Such temporal changes in the response of schizophrenics to information, reflected in findings of the "redundancy deficit" or reaction time crossover phenomenon (Bellissimo & Steffy 1972; DeAmicis & Cromwell 1979; Rodnick & Shakow 1940), are not discussed. Also missing is the huge body of data and theory which focuses upon stimulus input (e.g., Venables 1964) as the primary dysfunction in schizophrenia. The authors refer to selective attention and responses to novel stimuli, but little reference is made to the formation of the percept (or other internal representation) which precedes execution by the motor system (e.g., Knight 1984). This may be partly a consequence of the reliance on animal data. Using a forced-choice, target detection method for assessing the span of apprehension, Elkins (1989) found that backward masking of distractor elements further impairs schizophrenics, while depressives and normals profit from this same procedure. Reviews of the information-processing literature in general (Nuechterlein & Dawson 1984),

or the span of apprehension literature in particular (Asarnow et al., in press) indicate that such early processing events are frequently impaired in schizophrenics.

Gray et al. should be complimented not only for their emphasis on cognitive deficit in schizophrenia, but especially for their choice of its most powerful explanatory instances, that is, instances wherein the performance of schizophrenics is superior to normal or counterintuitive as a generalized cognitive deficit. The latent inhibition, Kamin blocking, and PREE effects are such instances, and there are reports of other tasks on which schizophrenics (particularly paranoid schizophrenics) perform better than normals. These include a superior ability to respond to a secondary message in a dichotic listening task (Spring 1985), and greater incidental recall of distractor elements following a Muller-Lyer illusion task (Kar 1967; also, see Cromwell 1968). All of these effects could presumably result from overattention to apparently "irrelevant" stimuli, a possible consequence of Hemsley's proposed deficit (sect. 2, para. 6), but in any case, they are theoretically significant.

Our conclusions are the following: (a) It is not yet clear whether the imaginary Christmas tree as conceptualized can hold all the ornaments. (b) More ornaments are probably needed before the celebration. (c) In any case, this model represents a highly commendable, stimulating, and provocative endeavor, and a sound contribution to the field.

In what context is latent inhibition relevant to the symptoms of schizophrenia?

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A few years ago articles of this sort would have been unthinkable. For most psychologists, schizophrenia either did not exist or was a social disorder of no interest to hard-headed experimental psychologists. Today, schizophrenia is unquestionably a disorder of the brain (however caused) and, as such, it provides one of the most exciting challenges for linking brain and cognition. Schizophrenic symptoms reflect disorders of consciousness, self-awareness, and social interaction and thus involve the highest psychological functions. In spite of the undoubted complexity of these functions, many of us believe that it is at last becoming possible to study them objectively and to relate them to brain processes.

The contribution from Gray and his colleagues contains a prescription for research on schizophrenia very much along the lines I have also proposed (Frith & Done 1988; Frith & Frith, in press). In this research programme the starting point must be the symptoms of schizophrenia and not the diagnostic category of schizophrenia. The symptoms have the advantage of remaining relatively well defined even if the diagnosis shifts back and forth with changing fashions. It is not the symptoms themselves that we should be examining, however, but the cognitive abnormalities that underlie them, for it is cognitive processes rather than symptoms or surface behaviour that will map onto brain function. These cognitive processes must be described in such a way that they can be readily linked to the function of brain systems. Furthermore, if we are to study links between brain and cognition in a truly experimental fashion it will be necessary to use animal studies. Thus it is very important to formulate the cognitive processes in terms that are applicable to animals as well as people.

In outline, this is what Gray and his colleagues have attempted to do. I admire the attempt, but I am critical of the details.

I shall say nothing about the neuroanatomical considerations and the various circuit diagrams that are proposed. My feeling is that this level of detail is not appropriate to our current knowledge of brain abnormalities in schizophrenia. I would find the circuit diagrams more convincing if the verbal descriptions of how they operate were backed up by a computational model.

The three tasks considered by Gray and his colleagues (latent inhibition, Kamin blocking effect, and the partial reinforcement extinction effect) have been chosen partly because they may be relevant to the symptoms of schizophrenia, but mainly because the dopamine system is implicated in their performance. Gray and his colleagues conclude that an overactive dopamine system results in "over-attention," that is, the subject attends to all stimuli, whatever their importance. I am not convinced that this accounts adequately for the results. In particular I would expect a perceptual disruption that serious to impair acquisition in the non-pre-exposed group. This learning also requires the animal to pick out a stimulus, but strangely enough, this is not disrupted by amphetamine. A more adequate view is to be found in the elegant work of Ridley and Baker on the effects of amphetamine on reversal learning in the marmoset. Here too an asymmetry is found, in that initial learning is unimpaired by amphetamine, but reversal is severely disrupted (Ridley et al. 1981). More detailed analysis of this phenomenon showed that, under amphetamine, animals learned about the "valence" of objects (whether they were nice or nasty) normally, but had great difficulty in inhibiting their responses to this valence when the responses became inappropriate. These results are best explained in terms of two learning systems that operate at different levels. The lower level system learns about the properties of objects (colour, niceness, familiarity, etc.). These are relatively permanent properties of objects and so this knowledge can only be altered slowly. Acquiring it is unaffected by amphetamine. The higher level system acquires knowledge about objects which is temporary and arbitrary and can override the lower level system. This enables the animal to think, "I know this object is nasty, but in the current circumstances I shall approach it." This higher level cognitive process permits rapid reversal learning and is disrupted by amphetamine. The importance of this view is that it enables us to think more clearly about what is meant by "relevance." Even though the distinction between relevant and irrelevant stimuli is a crucial component of the model presented by Gray and his colleagues, little attempt is made to explain this concept.

The most obvious aspect of relevance is that it is a property of neither the stimulus nor the response. Whether or not a stimulus (or a response) is relevant depends on the context. Effects of context have been studied extensively using tasks of the form: if A do X, if B do Y. These tasks explicitly use context to determine the relevance of a stimulus or a response. Learning of such tasks is impaired by lesions of prefrontal cortex (e.g., Petrides 1987) and by disruption of cholinergic inputs to the hippocampus (e.g., Ridley et al. 1989), implicating brain regions considered relevant to schizophrenia by a number of authors (e.g., Frith & Done 1988) as well as by Gray and his colleagues.

Change in relevance is not always explicitly indicated by a changed context. Often the context has to be inferred. This is most striking in human communication. Sperber and Wilson (1987) consider that the principle of relevance is fundamental to understanding how communication works. It is not sufficient to know what the words mean. It is necessary to infer their relevance in the context of the beliefs and intentions of the speaker and the listener. Thus the two knowledge systems implicated by Ridley and Baker's work also apply to the higher level cognitive processes involved in verbal communication. We have to distinguish between what words mean and their relevance (what they signify). This has long been recognised as a problem for schizophrenic patients. Their semantic memory system is largely intact in that they know what words mean. However, they have difficulty in inferring which meanings are relevant in a particular context. As a result, they do not inhibit irrelevant meanings.

The failure of some schizophrenic patients to show latent inhibition implies that they continue to attend to stimuli when this is no longer appropriate. This could be described as a failure of habituation. Habituation of the orienting response has been extensively observed in schizophrenia without leading to any clear conclusion (Zahn et al., in press). Habituation is thought to reflect a number of different processes, including nonspecific arousal, stimulus identification, and stimulus significance (e.g., Frith et al. 1988). It follows that in the latent inhibition task there are also many different processes involved, only some of them relevant to schizophrenic symptoms. Hall and Honey (1987) have shown that context effects have much more influence on latent inhibition than they do on habituation. This is fortunate for Gray and his colleagues. Studying tasks which involve the processes by which context determines relevance will enable us to understand the symptoms of schizophrenia. A more detailed cognitive analysis suggests that latent inhibition may indeed be one such process, and it shows how this may relate to other processes more obviously relevant to schizophrenic symptoms.

Novelty value in associative learning

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Gray et al.'s target article summarizes the considerable converging evidence that the mechanism mediating learning in a small collection of two-stage learning paradigms – latent inhibition, the partial reinforcement extinction effect, and blocking – is also disrupted in schizophrenia. The behavioural experiments play a key role in the theory as a whole, serving as a bridge between neurophysiological dysfunction in rats and acute schizophrenic psychopathology. It becomes important, then, to scrutinize the purported correspondence between these three experimental effects and (a) the putative cognitive underpinnings of schizophrenia and (b) the putative underlying neurophysiological mechanisms.

Interferences in the three learning effects are said to have high "face validity" as models for the cognitive disorder. This assertion rests on Hemsley's hypothesis (1987a) that underpinning the symptoms of acute schizophrenia is a "weakening of the influence of stored regularities of previous input on current perception." On this basis alone, however, not only the above three paradigms but all conditioned learning requiring more than one trial to be acquired should be depressed, since the expression of any conditioned response requires the effective use of stored regularities. At the very least, learning in all two-stage phenomena (e.g., normal extinction) should show impairment, requiring as it does a memory in stage two of the regularities that obtained in stage one. Thus the Hemsley model does not really endow the three behavioural paradigms that *are* affected with an especially large measure of "face validity" as animal models of schizophrenia.

The relationship between the neurophysiological and behavioural levels is more precisely delimited in the target article, but it requires further clarification. Of the two roles accorded to the subicular-n. accumbens pathway, its monitoring of "novelty" is the one that is said to be responsible for controlling the behavioural regularities normally exhibited in the three paradigms. It appears, however, that two separate interpretations of novelty are conflated in the target article. In the first, an event is novel because it has been presented infrequently, or not at all, in the recent past. In the second, novelty is detected when the consequences of an event are unexpected. It follows that any learning increment or decrement resulting from the first type of novelty is nonassociative, the second being associative. The two types of novelty are not interchangeable: A good example is the nonoccurrence of an expected stimulus that is the key event in the partial reinforcement extinction effect. From a purely nonassociative standpoint, there is no novelty; the organism has considerable experience of the unconditioned stimulus not being present. What is novel is not the occurrence of nothing itself, but the inconsistency of the conditioned stimulus as a predictor of future events.

The authors do, in fact, make their own distinction between two types of novelty. When the novel stimulus occurs at random with respect to the ongoing motor program, the response habituates with the stimulus' repeated presentation (i.e., nonassociative learning). When the novel stimulus bears a reliable relationship to the motor program, its expected occurrence comes to be built into the motor program (which implies associative learning). But following along these lines, latent inhibition would appear to be a case of nonassociative learning, since in the pre-exposure stage, the novel event occurs at random with respect to whatever motor programs may be in operation. Thus the distinction drawn in the article between the two responses to novelty is not in one-to-one correspondence with the division between associative and nonassociative forms of learning.

It can be and has been argued that the same mechanism mediates both associative and nonassociative learning in general (Gluck & Thompson 1987; Hawkins & Kandel 1984) and latent inhibition and habituation in particular (Wagner 1976). If this is the position the target article adopts, then it ought to be stated explicitly, for it is still too controversial to be accepted as an unstated, theoretical given. Indeed, the idea that latent inhibition is governed by the same principles as habituation has received only equivocal empirical support (Hall & Channell 1985a), and has been questioned on theoretical grounds (e.g., McLaren et al. 1989).

In the light of this ambiguous evidence, it may be advisable to stick to an associative definition of novelty in endeavouring to explain the three learning phenomena by a common mechanism. In fact, the associative aspect of the authors' novelty mechanism bears a very striking resemblance to the Pearce & Hall (1980) model of associative learning. The major innovation of their model, which resonates with the target article's novelty mechanism, was that the associability of a stimulus is related to the extent to which it predicts its consequences. Thus, stimuli that fully predict their consequences will not receive further processing. In addition, in exactly the same way as the target article, Pearce and Hall (1980) contend that the diminishing of attention towards a stimulus that predicts its consequences reflects a switch in the mode of information-processing from controlled to automatic.

Thus we have the interesting and testable possibility that the subicular input to the n. accumbens is the neurophysiological substrate of the comparator in the Pearce-Hall model, which measures predictability. The problem remains, however, that the Pearce-Hall model can account for a much wider range of associative learning phenomena (e.g., simple acquisition and conditioned inhibition) than the limited collection that is enumerated by Gray et al. as being disrupted when the subicular-n. accumbens pathway is cut. Further efforts are required to pinpoint, within a general theory of associative learning, the mechanism or mechanisms that are rendered dysfunctional by the schizophrenic disorder. In this way we may better be able to integrate the cognitive, behavioural, and neurophysiological data.

Schizophrenia and stored memories: Left hemisphere dysfunction after all?

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Gray et al. propose "a failure in schizophrenia to integrate stored memories of past regularities of perceptual input with ongoing motor programs in the control of current perception" as the critical feature of schizophrenia. The distinction between perceptual novelty and stored memories is central to their target article. This distinction is also central to some recent ideas about hemispheric specialization. Goldberg and Costa (1981) proposed that the right hemisphere is critical for exploratory processing of novel information and the left hemisphere for processing mediated by well-established representations.

The analysis of perceptual deficits called agnosias provides powerful evidence in support of the left hemisphere's role in the use of stored knowledge (Goldberg 1989; 1990). Two types of agnosias exist: *apperceptive* and *associative*. In apperceptive agnosias, perceptual constancies, that is, the ability to identify changing stimulus patterns as representing stable physical objects under diverse sensory conditions, are disrupted. In associative agnosias, the ability to identify specific exemplars as members of generic categories is disrupted. Associative agnosias involve an inability (for whatever reason) to connect the on-line, unique, and ever-changing perceptual patterns with pre-existing, stored, stable, generic representations. They are, in a sense, semantic amnesias. Teuber (1968) referred to associative agnosias as "percepts stripped of their meaning." The phenomenal accounts of schizophrenic experiences quoted by Gray et al. (sect. 2, para. 3) also emphasize perceptions devoid of meaning. Are the positive symptoms of schizophrenia manifestations of an associative agnosia neurodevelopmental rather than acquired?

The perceptual processes disrupted in the two forms of agnosia, associative and apperceptive, are cognitively complementary. They are also complementary neuroanatomically. Both apperceptive and associative agnosias may be caused by bilateral lesions to the posterior cortices or the underlying white matter. They may also be caused by unilateral lesions and then a clear complementarity emerges. Apperceptive agnosias may be caused by posterior right hemisphere lesions but never by left hemisphere lesions. Associative agnosias may be caused by posterior left hemisphere lesions but never by right hemisphere lesions (for review, see Goldberg 1990). What does it tell us about the functions of the left hemisphere? That it is critical for the application of stored generic memories to the interpretation of ongoing perceptual inputs. In other words, the left hemisphere is critical to our ability to interpret very large, and for practical purposes infinite numbers of perceptual constellations, as representatives of a finite number of prespecified classes of equivalent objects. Are the positive symptoms of schizophrenia linked to the posterior portion of the left hemisphere?

Gray et al. imply that it is important to understand schizophrenia in an evolutionary context, namely, to relate it to some basic deficit which is more fundamental than language impairment and can be elicited in animals. I welcome this emphasis on evolutionary continuities rather than discontinuities and have espoused it in the discussion of hemispheric specialization (Goldberg & Costa 1981; Goldberg 1990). The novelty-routinization dichotomy of hemispheric specialization is more general and more fundamental than the traditional distinction between language-based and nonlanguage-based processes. Language is but a special case of a well-routinized representational system, and the novelty-routinization distinction is applicable in any species capable of learning. Associative agnosias are *not* secondary to language deficit. They may occur without aphasias, are linked to neuroanatomical territories adjacent to, but distinct from those of aphasias, and are caused by the disruption of perceptual processes which are already present in animals. Associative agnosias are modality-specific. The very existence of associative agnosias, then, reflects the multiple nature of generic, categorical representational systems, not all of them reducible to natural language. Their link with the left hemisphere enables one to enlarge on the functions of the left hemisphere in a nontrivial way. The left hemisphere is critical for any process mediated by well-routinized, stored, generic representations, linguistic and nonlinguistic alike.

Gray et al. relate schizophrenia to temporal lobe pathology (sect. 3, para. 2). Both visual and auditory forms of associative agnosia are caused by lesions at various points along the occipito-temporal axis of the left hemisphere. The territory of visual object agnosia is similar to the territory of the "what" system in monkeys (Mishkin et al. 1983), but limited to the left hemisphere.

Gray et al. assume that the positive symptoms of schizophrenia are related to dopaminergic hyperactivity (sect. 3, para. 2). A growing body of evidence exists that dopamine pathways favor the left hemisphere over the right (for review, see Tucker & Williamson 1984). It is then logical to assume that a neurodevelopmental aberration of dopamine systems will have a particularly strong effect on the left hemisphere.

Is schizophrenia a left-hemisphere disease, after all? Scientific fads change. Once upon a time there used to be more talk in the schizophrenia literature about the left hemisphere than about the frontal lobes, but it seems that lately it has been the other way around. By putting together Grays et al.'s "neuropsychology of schizophrenia" and my own "neuropsychology of hemispheric differences," are we forced, unwittingly, to go the full circle?

I have been quite vocal in arguing that physiological and cognitive "hypofrontality" is about as specific in brain disease as fever is in bacterial infection, and that its presence in schizophrenia is therefore not very illuminating (Goldberg 1985; Goldberg & Bilder 1987). Does this mean that I do not believe that schizophrenia is *essentially* a frontal lobe disease? Not necessarily. I am only saying that the presence of "hypofrontality" is in and of itself rather weak evidence to support this notion. But if Weinberger (1987) is right in proposing a neurodevelopmental aberration of the mesocortical dopamine system (known to target in particular the prefrontal cortex) in schizophrenia, then the consequences of the parallel mesolimbic dopamine effects may well be (at least somewhat) lateralized to the left hemisphere. Dopamine may yet prove to be the great conciliator, tying together the frontal lobe and left hemispheric views of the schizophrenic disorder into a unitary theory. In this grand scheme of things, I will leave the challenge of integrating the striatal, limbic, and neocortical (a bit neglected in this paper) elements of the puzzle, and its negative (frontal lobes?) and positive (left temporal lobe?) components, to someone else. Gray et al., part two?

The role of long-term memory (LTM) and monitoring in schizophrenia: Multiple functions

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Gray et al. have presented a thought-provoking model which integrates neurophysiological mechanisms with select characteristics of schizophrenia, focusing on positive symptoms. The interactive nature of neuropsychological mechanisms and the

complexity and variability of schizophrenic cognition and behavior demand a multifactor model. Gray and colleagues have proposed one. The model is speculative, depending on neurophysiological mechanisms that have not been well worked out.

Attempts to understand neuropsychological mechanisms in disorders as complex as schizophrenia have been made for many years. Different brain regions and cerebral deficits have been emphasized at various times. Currently, interest in anterior frontal regions, implicating the dorsolateral prefrontal cortex, has emerged as one promising focus of abnormality. Despite this research emphasizing the anterior frontal cortex, and Gray and colleagues' emphasis on the septohippocampal system and its projections, there are still major gaps in our knowledge of the details associated with many of the neural pathways involved in human cognition.

The role of long-term memory (LTM) and monitoring is a key aspect of the view of the psychology of schizophrenia proposed by Gray et al. Using Frith's and Hemsley's models, they propose that willed intentions are not properly monitored in schizophrenia. Gray et al. link this to a weakening of LTM. As a consequence, actions can occur without any awareness of what *elicited* them. This model is used to explain hallucinations.

Gray et al. emphasize cognitive functions linked to LTM. However, a weakening of LTM in schizophrenia, as proposed by Gray et al., affects other related aspects of these patients' cognition, and is a factor in schizophrenics' strange behavior. In addition to difficulties in awareness by a patient of what elicited his behavior, problems with LTM can result in impaired perspectives about what is appropriate and what is inappropriate in a specific situation.

Thus, one way that we use LTM is to give us some perspective on consensually appropriate ways to behave in the specific situation one faces, and to suggest which behaviors should be avoided because they are regarded as strange. People use this particular function of LTM on a moment to moment basis, in an effortless manner, usually without being consciously aware of it. A perspective on what behaviors and thinking are appropriate serves as one dimension in the complex matrix of factors important for reality testing. Evidence on impaired perspective suggests that it is one of several important factors involved in schizophrenics' disordered thinking (Harrow et al. 1989; Harrow & Quinlan 1985) and delusional ideation (Harrow et al. 1988).

While the focus of Gray et al. on where hallucinations come from involves one important aspect of hallucinations, an equally important aspect of delusions and thought disorder concerns why schizophrenics believe their hallucinations and delusions to be real. Other evidence from Posey and Losch (1983–84) suggests that over 50% of normals have experienced brief, mild hallucinations. We would propose that normals discard occasional mild hallucinatory experiences because of stored knowledge that these experiences are not linked to real events. LTM about the world and about consensual norms sets limits for normals on the extent of their unreal thinking and behavior. This type of monitoring usually occurs below the level of awareness.

For normals, unreal thoughts do not usually emerge into awareness because of their adequate perspective about what is appropriate. When unreal thoughts occasionally emerge into awareness for normals, or when normals occasionally experience hallucinations, they can discard or correct them, based on stored knowledge about what is real and what is appropriate. From this viewpoint, perspective about what is appropriate, dependent on LTM in moment to moment situations, is involved in executive processes and serves control functions.

Evidence also indicates that the less effective use of LTM by schizophrenics and psychotic patients is selective, because schizophrenics' judgments of social appropriateness are improved when they evaluate the appropriateness or reality of *other* patients' behavior. These results suggests that the LTM of schizophrenics on standards of appropriateness may be adequate, but when applied to their own behavior during acute upset, or during acute disorder, stored knowledge of consensual norms is not used effectively.

We have suggested that during acute disorder patients – and normals – are influenced by their internal nonshared context (e.g., their personal concerns and needs) and are less likely to attend to demands of the objective external context or social situation. This research suggests that LTM is not permanently impaired in schizophrenics, but how effectively it is used depends on such factors as the setting, the type of stimulus situation encountered, its affective loading for the person, and the person's level of arousal (Harrow et al. 1989).

Another component of the cognitive-psychological model of Gray et al. concerns problems in selective attention involving over-attention and difficulty in distinguishing figure-ground relationships. Gray et al. present several examples of this disorder in selective attention. However, evidence from a series of experiments using schizophrenics, nonschizophrenics, and normals indicates that although a difficulty in selective attention is found in many (but *not* all) schizophrenics, it is also found in nonschizophrenic patients and in normals, especially when they are upset (Harrow & Quinlan 1985, pp. 270–92).

A cardinal principle for neuropsychology, with implications for schizophrenia and mania

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The target article gives a valuable integrated review of some of the best in neuropsychology, but it also reveals that this science is mainly empirical, with only a hodge podge of isolated hypotheses for theory. If neuropsychology is to serve as a foundation for psychiatry, if it is to become a science with genuine explanatory power, a coherent theoretical structure must be erected. I maintain that this structure should take the form of a neural network theory, and indeed, a toolbox of neural network principles, mechanisms, and architectures is already available to get the construction started. Like theoretical physics, network theory embodies empirical observation and theoretical analysis in mathematical models. This is essential for quantitative science. However, the mathematical theory also has a qualitative component derived in part from its empirical interpretation, and qualitative analysis is an essential prelude to mathematical modeling. This qualitative aspect of network theory is what I wish to emphasize here.

Networks in neuropsychology must have two complementary interpretations: *psychological* on the one hand and *neurological* on the other. I wish to show that, in both domains, network theory gives us new insights into the nature of mental disorder. In the psychological domain it provides an explanatory framework for psychoses, and in the neurological domain it implicates a particular class of neural mechanisms in the origins of psychoses.

1. Some pattern processing principles. As the cardinal principle of theoretical neuropsychology, the starting point for a coherent theory, I suggest a working hypothesis about the way information is represented in the brain. On the presumption that the brain has a modular structure, with each module dedicated to some specialized information processing task, the principle asserts that *in each brain module information is represented by a neural activity pattern.* This is no new idea, of course, but its implications are better realized by making it a theoretical centerpiece. To begin with, it should be contrasted with the

alternative view that information must be represented symbolically and processed algorithmically in the brain (Smolensky 1989), a view which has dominated cognitive science until quite recently. The cardinal principle is the starting point for a theory in which information processing is a dynamical process of pattern formation. The manifold characteristics of this process are determined by further assumptions about the structure and operation of the modules.

At the most general theoretical level, a module is modeled as a system of identical processing elements or *nodes*, corresponding, for example, to minicolumns in cortical modules. Apart from any internal structure that might be attributed to their nodes, modules with different functions share certain general properties which give them common pattern processing capabilities.

(A) Two different levels of pattern activation can be distinguished: First, a *subliminal pattern*, for which the activation of each node is below its firing threshold; psychologically, this can be interpreted as a *preparatory set* or *priming* in both sensory and motor modules. Second, an *output pattern* of nodes is activated above firing threshold; the information in such a pattern is transmitted to other modules.

(B) Pattern formation in a module is governed by *lateral interactions* among nodes, which must include a suitable admixture of excitatory and inhibitory connections to produce stable patterns.

(C) In some modules, output patterns can be stored in long term memory (LTM) by synaptic modification in accordance with Hebbian principles. They can be retrieved by nodal activations.

Modules with the above properties are capable of pattern selection, matching, mixing, and switching, as well as LTM storage and retrieval. The flexibility of their pattern processing is greatly increased by introducing a system of *gain controls* to regulate it. Moreover, a central gain control system serves to coordinate the processing of interacting modules. There is considerable evidence for the existence of such a system in the human brain, chemically coded by various transmitters, including dopamine, noradrenline, and serotonin. It has been suggested that *many mental disorders can be regarded as breakdowns in specific pattern processing capabilities caused by malfunctions in gain regulation* (Hestenes 1990). Let us see how this idea might account for some positive symptoms of schizophrenia.

Thought disorder can be understood as a breakdown in competitive pattern selection, with various characteristics depending on the module(s) in which the breakdown occurs. A typical module has a multitude of incompatible input patterns from other modules (including the "old memories" of the target article); these compete via lateral interaction for control of the module output. However, tuning of the competition by lateral gain adjustment enables a module to meet the conflicting processing requirements for different situations. High gain biases the competition in favor of the presently active output pattern and so reduces the possibility of pattern switching. This is one mechanism for *selective attention*. On the other hand, low gain greatly increases the tendency for pattern switching activated by subliminal patterns. The low gain state therefore enhances the search of associative memory for new possibilities. When the gain is too low, however, switching is excessive and the stability of pattern formation is lost. This suggests that thought disorder results from a malfunction in lateral gain control. Evidently it is most likely to occur in modules where the control of competitive selection is most critical. In modules controlling speech, for example, meaning may switch in midsentence and excessive influence of low level associations on word selection can produce fluent rhyming and punning.

Hallucinations can be attributed to a different type of gain control malfunction. There is now substantial evidence that visual mental imagery involves activation of the same modules activated in visual perception, with the major difference that primary visual cortex is coactivated only in the latter case (Farah 1989). Evoked mental images can presumably serve as "expectations" priming primary visual cortex for the detection of objects. According to Gestalt principles, a perceptual pattern, or *percept*, is a fusion of "top-down" expectation and "bottom-up" sensory input. This fusion will depend on the relative gain for the two input channels. Evidently, if the top-down gain is too strong it can produce percepts of objects not presented in the sensory input. This is a plausible explanation for visual hallucinations. A similar explanation may apply to the auditory hallucinations of schizophrenics.

2. Gain control mechanisms. Having sampled the potential of neural network theory for explaining psychological aspects of psychiatric disorders, let me turn briefly to the complementary problem of identifying the corresponding brain malfunctions. Beginning with the cardinal principle, network theory leads to the conclusion that we should pay particular attention to the various gain control mechanisms for pattern processing. More specifically, I have argued that *the primary cause of manic-depressive illness is a breakdown of gain control in the nucleus accumbens* governing the release of behavioral plans (Hestenes 1990). The target article suggests that the nucleus accumbens also plays a pivotal role in schizophrenia, though the malfunction is attributed to damage in the septo-hippocampal system. This is consistent with the fact that, in their acute phases, mania and schizophrenia can be difficult to distinguish on the basis of immediate symptoms alone. Both disorders are ameliorated by neuroleptic treatment, which is believed to lower dopamine controlled gain in the nucleus accumbens. The underlying difference seems to be that in schizophrenia the gain reduction compensates for a defect in the septo-hippocampal system, while in mania it compensates for a defect somewhere in the gain control system itself.

The fact that mania is often accompanied by psychotic symptoms such as delusions, paranoia, thought disorder, and, less frequently, hallucinations suggests that gain disregulation is not necessarily confined to the nucleus accumbens but can spread to other modules sharing a common gain control system. The characteristics of the associated psychoses are accordingly important clues to the underlying malfunction and can be profitably compared with schizophrenic symptoms. The symptoms of auditory hallucinations and thought control, so typical of schizophrenia, are rare in mania – further evidence that the disorders involve different modules. This lends indirect support to the contention of the target article that these particular symptoms derive from faulty monitoring of motor output.

Neural network theory also bears on the interpretation of the "circuit diagrams" and related neurological evidence in the target article. Gain control appears to be a ubiquitous feature of network design (Prochazka 1989). The target article fails to make the crucial distinction between modulatory connections and connections transmitting information (patterns). It fails to note that the very different processing functions of these two kinds of connection is reflected in very different topologies of circuit loops involving them (Percheron *et al.* 1989). Of course, our ignorance about these matters is great. I submit, nevertheless, that network theory tells us that gain control mechanisms must play a pivotal role in mental disorders. Surely we can look forward to deeper insights as the development of theoretical structure is joined to the planning and interpretation of empirical studies with the high quality of those reviewed in the target article.

The mechanism of positive symptoms in schizophrenia

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Gray et al.'s target article synthesizes an impressive array of studies and ideas relating neurocognitive defects to schizophrenia. Most of my comments derive from certain clinical observations and how they might relate to the research issues at hand.

The last schizophrenic I happened to interview prior to writing this commentary was 19 years old and had been seriously ill for approximately three years. One of his problems was that he was easily distracted by a variety of stimuli, for example, the faint sounds of laughter from an adjacent room. Moreover, he was paranoid, thinking that these people were laughing at him. Consistent with Gray et al.'s model of schizophrenia, these symptoms are also typical for amphetamine-induced paranoia.

So far so good. What made this patient clearly schizophrenic, however, was not paranoia *per se*, but repetitive, severely derogatory allegations about other people which he experienced as being put into his mind by an outside force, namely the devil. These thoughts dominated his own mentation, by his own estimation, at least 50% of each waking day. He could not turn them off, no matter how hard he tried (and try he did, ranging from banging his head against walls to incessantly praying). The malignant intrusiveness of these thoughts was demonstrated by his inability to carry on a conversation without being interrupted by 5–20 second episodes where he would stare off into space, unable to speak, later reporting that another "bad thought" had recurred. Gray et al. propose that a pigeon-holing defect is the primary cognitive disturbance in schizophrenia. It seems doubtful, however, that a pigeon-holing defect – which produces its ill effects by virtue of the *unexpectedness* of certain experiences – could have produced a symptom which was so frequent, so stereotypic, and so expected (for additional discussions see Hemsley 1987b; Hoffman 1986, 1987).

Gray et al. suggest that another cognitive defect, namely, a failure in monitoring intentions, may underlie positive symptoms corresponding to altered experiences of willfulness. If so, our patient may have actually intended to think negative thoughts about others; his monitoring difficulties would then cause these intentions to be experienced as involuntary. Although this is a possible explanation, it seems unlikely because the patient did not suffer from a broad range of involuntary thoughts and actions, which would be the consequence of a general defect in monitoring intentions. Instead, the nonself, controlled-by-the-devil attribute was associated only with a very narrow range of experience, namely, thoughts that contained negative allegations about other people. This suggests that the experiential involuntariness of these episodes is not a general monitoring failure.

Perhaps a lesson can be drawn from a neurological disorder described by Goldberg (1985). These patients suffer from lesions of the supplementary motor area (SMA) of the frontal lobes; this cortical area is required to initiate purposeful motoric actions. SMA lesions can result in repetitive actions which are initiated independently of the "will" of the subject. These patients may, for instance, develop "alien hands" which seem to have acquired purposes of their own that are out of their control. The hand may attempt to unbutton the patient's clothing when the subject experiences no intention to do so. This syndrome can produce a kind of psychosis in which patients come to believe that their arms have been possessed by an alien, nonself force (Goldberg, personal communication). The problem here is not simply that the motor behavior is experienced as involuntary,[1] but that the motor behavior demonstrated its own autonomous purposefulness.

Along these lines, the schizophrenic patient's psychosis was not simply due to the fact that he had involuntary thoughts; it was because he experienced them as having their own autonomous purpose, namely, to turn him against other people. Analogous to the "alien hands syndrome," perhaps such positive symptoms in schizophrenia also derive from an abnormality in the initiation of "mental actions" at a cortical level (see Hoffman & Dobscha 1989 for one such model).

The remainder of my comments relate to pharmacology.

First, it is now clear that extensive blockade of CNS dopamine receptors occurs immediately after the administration of the first dose of the antipsychotic drug (Farde et al. 1986); clinical improvement, however, generally requires several days to a week or more of drug exposure (Bunney 1984). This suggests that factors other than simple dopamine receptor blockade contribute to the therapeutic action of these agents.

Second, there is still very little direct evidence of dopamine receptor elevations in the brains of schizophrenics that are not secondary to neuroleptic exposure. Although the positron emission tomography (PET) study by Wong et al. (1986) supported this hypothesis, later PET studies have failed to confirm this claim (Farde et al. 1990; Martinot et al. 1990).

Third, the assertion that acute schizophrenics and not chronic schizophrenics suffer from positive symptoms is wrong. Chronically ill patients may have sustained positive symptoms such as thought disorder, hallucinations, and delusions. This makes me wonder whether the chronic patients who were found to demonstrate normal levels of latent inhibition (Baruch et al. 1988) were in fact free of positive symptoms as predicted by the hypothesis.

Finally, there is another pharmacological agent that can induce a schizophrenic-like psychotic state: phencyclidine (PCP). In certain vulnerable individuals the psychosis can look very similar to schizophrenia. The receptor for PCP appears to be distributed in a pattern which almost exactly mirrors the NMDA receptor in the mammalian CNS (Maragos et al. 1988). The NMDA receptor is one of at least three receptor subtypes for the excitatory amino acid, glutamate; PCP appears to inhibit the action of glutamate at the NMDA receptor (Duchen et al. 1985). Relevant to Gray et al.'s discussion, very high concentrations of the NMDA and PCP receptor are in CA1 of the hippocampal formation, with moderate concentrations in entorhinal and other cortical areas, and low concentrations in the subiculum (Maragos et al. 1988). How might the authors incorporate these findings into their model? It is of interest that PCP-induced psychosis frequently responds poorly to dopamine-blocking agents.

In summary, while the neurocognitive model presented by Gray et al. is an important step forward, I believe that other factors are active in causing positive symptoms in schizophrenia. In many cases these symptoms are relatively stable and circumscribed in content (including not only delusions but hallucinations as well, cf. Hoffman 1986, pp. 513–14); this suggests that a small number of "messages" are being selectively reproduced from some sort of memory storage. I don't see how a general impairment in ordering perceptions or monitoring actions can slavishly re-activate a particular message or memory. Moreover, I believe that questions should be raised about the postulated central role of dopamine excess in causing positive symptoms. This is not to discount the critical importance of dopamine-blocking agents in the treatment of positive symptoms. However, it may be that dopamine blocking agents, like most pharmacological agents in medicine, compensate for pathology expressed at other physiological levels.[2]

NOTES

1. Simple motor tics, for instance, are experienced as involuntary but do not generally trigger psychotic reactions. The repetitive thoughts of

patients with obsessive-compulsive disorder can acquire alien, nonself attributes, though this is rather infrequent. In general, the patient still endorses the goal of the repetitive thoughts and actions as his own (e.g., to remain clean); his distress derives from his inability to stop implementing plans to accomplish the goal.

2. Along these lines, a neural network simulation by Hoffman and Dobscha (1989) shows how down-regulation of mesocortical dopamine can block "parasitic messages" produced by a dysfunctional cortex by upgrading the specificity of input information required before a cortical output is generated.

A neuropsychology of psychosis

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Attempts to understand the pathophysiology of schizophrenia continue to be hampered by a lack of definitive diagnostic tests and by the absence of animal models of the illness. Whereas we have evidence that genetic factors play a role in schizophrenia (Kety et al. 1968), the location of the specific gene or genes and the gene products (or absence of products) responsible for the syndrome remain obscure.

One approach, that chosen by Gray et al., is to focus on one aspect of schizophrenic illness in an attempt to understand at least part of the schizophrenic syndrome. A potential pitfall of a focused approach is that the part may be taken for the whole, such as here, where the acute, positive symptoms studied become "schizophrenia" in the title and section headings (sect. 1; 2; 3) of the target article.

Gray et al. focus on the "primary positive symptoms of acute schizophrenia" (sect. 2, para. 2) with a "main aim . . . to describe how an excess of dopaminergic activity can produce the symptomatic picture of acute schizophrenia" (sect. 2 para. 1). While a detailed, testable model that links molecular, cellular, and behavioral levels of analysis is presented, the explicated behaviors may be closer to what would be called psychosis rather than the clinical syndrome of schizophrenic illness. Psychotic behavior is not unique to schizophrenia, and previous exploration of altered brain dopamine function (Swerdlow & Koob 1987a) has implicated psychosis rather than schizophrenia as the consequence of dopaminergic hyperactivity.

Amphetamine induced dopaminergic hyperactivity is not a particularly accurate model of schizophrenic illness. Snyder (1972) has pointed out that while amphetamine psychosis may be useful as a model of paranoid states in schizophrenia, it differs in major ways from most schizophrenic illness. In contrast to schizophrenia, amphetamine addicts may be hypersexual; they may fail to display flattened affect, lack formal thought disorder, and fail to demonstrate symptoms of any but the paranoid form of schizophrenia.

Amphetamine psychosis as a model of even a narrow form of paranoid schizophrenia also inculpates more than dopaminergic hyperactivity. Snyder (1972) and others (Kokkinidis & Anisman 1981) have stressed the multiple effects of amphetamine on brain neurotransmitters, with both norepinephrine and dopamine activity altered following amphetamine administration.

Two other aspects of schizophrenic psychopathology need explication before there can be a neuropsychology of schizophrenia. First, in addition to the acute and chronic manifestations of schizophrenia, a less severe but schizophrenia-like syndrome has been observed in the biological relatives of schizophrenic individuals (Kendler 1985; Ingraham & Kety 1988). While these individuals are free of psychosis (and presumably free of impaired latent inhibition), they appear to share a pathology with their chronic schizophrenic relatives. Second, there is the possibility that some schizophrenia is nonfamilial, with a primarily environmental etiology (Murray et al. 1985). Clarifying the neuropsychology of these variants of schizophrenia would illuminate the core syndrome as well.

Relabeled as a neuropsychology of psychosis, the work of Gray et al. presents several opportunities for further understanding schizophrenic illness. Is the deficit in latent inhibition (Baruch et al. 1988) unique to acute schizophrenia, or is it also found in psychotic affective illness? If it is unique, then a definitive diagnostic test for schizophrenia may be at hand. Is the deficit in latent inhibition present in the prodrome, perhaps leading to preventive approaches? Likewise, is any form of the deficit observable, and useful as a marker, in the biological relatives of affected individuals?

In summary, while the model of Gray et al. might be better labeled, it usefully integrates multiple levels of neuropsychopharmacological investigation and suggests fruitful future approaches to the puzzle of schizophrenia.

Excitatory amino acids, NMDA and sigma receptors: A role in schizophrenia?

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The search for the underlying mechanisms of schizophrenia in organic brain pathology has a lengthy history, producing a plethora of results which implicate almost every area and system in the brain (for review: Berman & Weinberger 1989). It is impossible to propose a useful model of schizophrenia, even if we confine ourselves to the "acute" positive symptoms, without ignoring the larger part of this data. The model proposed by Gray et al. is thus necessarily selective in its focus. As a consequence, it is also precise and can be tested by relatively straightforward experimentation that we hope will improve our understanding of the syndrome and will certainly provide new data about the structure, function, and neurochemistry of the limbic-diencephalic systems.

We will consider here several relatively new avenues of investigation which are closely related to the model presented and appear worthy of the spotlight.

The first of these is the possible role of the sigma (σ) receptor. It has recently become clear that this binding site is not an opioid receptor as previously believed, nor is it synonymous with the phencyclidine (PCP) binding site on the N-methyl-D-asparate (NMDA) receptor (Sonders et al. 1988). An observation central to the dopamine hypothesis is the beneficial effect of neuroleptics, which are dopamine receptor antagonists, on the signs and symptoms of psychosis (Carlsson 1988). These drugs are used to correct the effect of amphetamine in the cognition experiments described. It is now clear, however, that these neuroleptics have an affinity for sigma receptors which is often equal to, if not greater than, their affinity for dopamine receptors (Downes et al. 1986; Tam & Cook 1984). The metabolites of haloperidol, for example, have a considerably higher affinity for sigma than for dopamine receptors, and as metabolism proceeds the sigma effects are apparently predominant over the dopaminergic effects (Bowen et al. 1990). Sigma receptors show a marked response to the chronic administration of neuroleptics, with haloperidol causing a dramatic down regulation after 14 days (Itzhak & Alerhand 1989). Largent et al. (1988) have tested a group of promising, novel antipsychotic drugs for binding characteristics to seven different receptors. The only common feature amongst the different drugs was a high affinity for sigma sites. Sigma receptors are dense in the human nucleus accumbens (Weissman et al. 1988) and other limbic areas, as well as over the striosome projecting zone of the substantia nigra, pars

compacta (Graybiel et al. 1989) and many other areas centrally involved in the model under discussion (Contreras et al. 1987; McLean & Weber 1988; Gundlach et al. 1986; Jansen et al. 1990).

Sigma receptors appear to play a significant role in the regulation of the dopaminergic system. For example, selective sigma ligands such as di-ortho-tolylguanidine (DTG) inactivate nigral dopamine neurons (Steinfels et al. 1989) while the A10 mesolimbic system can be activated by the sigma agonist N-allyl-normetazocine, (+)SKF10,047 (Freeman & Bunney 1984). This activation can be blocked by the selective sigma ligand rimcazole, which has demonstrated antipsychotic properties (Ceci et al. 1988). One of the possibilities raised by these results is that dopaminergic over-activity arises from excessive activation of A10 dopamine neurons by endogenous sigma ligands. Such endogenous ligands, variously called sigmaphins and endopsychosins, have been discovered in the brain (Contreras et al. 1987; Su et al. 1986).

In addition to antipsychotic drugs, such psychotomimetic substances as phencyclidine and ketamine also bind to sigma receptors. It has been suggested that phencyclidine-induced psychosis may be one of the best models of schizophrenia in man (Allen & Young 1978; Domino 1981; Snyder 1980). It is thus apparent that an experimental model based upon the effects of neuroleptics must recognise the fact that a substantial fraction of the binding will be to sigma receptors. There is increasing reason to suppose that these receptors may come to play an important role in our neurochemical models of schizophrenia.

Gray et al. describe thought disorder as possibly arising when nonintegration of current contextual data with stored data weakens moment-by-moment associations between elements of the stream of discourse, leading to abnormal associations. It is of interest to recall that phencyclidine is specifically described as a "dissociative" anaesthetic/hallucinogen, a category distinct from the "psychedelic" drugs represented by the serotonergic inhibitor, LSD-25 (Grinspoon & Bakalar 1981). Using the cognitive model, Hemsley describes hallucinations as "intrusions into conscious experience of material from long-term memory (LTM), this then being attributed to an external source" (Hemsley 1987a) whereas George & Neufeld (1985) note that, in normal circumstances, sensory processing has an inhibitory effect on the spontaneous retrieval of information stored in LTM. These concepts are very similar to those used to explain the dissociated, hallucinatory state resulting from sensory deprivation (West 1975) and arising in the "near death experience" (Jansen 1989; 1990), two states which arise *de novo* and may thus be due to endogenous "dissociative" substances.

The excitatory amino acid (EAA, chiefly glutamate and aspartate) systems loom very large in the model, being the neurotransmitters of many key pathways in this model. Phencyclidine binds not only to sigma sites but also to a binding site on the NMDA receptor, a subclass of EAA receptors which has been strongly implicated in the formation and retrieval of memories and other aspects of cognition (for a review: Monaghan et al. 1989). It seems likely that models involving abnormalities of normal learning and memory will involve NMDA receptors, which are very dense in the human septo-hippocampal system (Jansen et al. 1989a; 1989b). Because phencyclidine functions as an NMDA receptor antagonist, it is possible that the EAA system is underactive in schizophrenia (Etienne & Baudry 1987; Kim et al. 1986). This could result from an excess of the phencyclidine-like substances that have been identified in the brain (Zhou et al. 1988). EAA hypofunction could also result from damage to presynaptic EAA terminals, from postsynaptic damage due to the excitoxic/abnormal neuronal plasticity mechanisms suggested by Olney (1989), or from an excess of dopamine (see below). In one study, increased [^{3}H]MK801 (a phencyclidine analogue) binding has been noted in all areas of the schizophrenic brain examined (frontal cortex, hippocampus, putamen, entorhinal region, and amygdala), reflecting a possible NMDA receptor upregulation due to presynaptic hypofunction (Kornhuber et al. 1989). MK801 appears to be highly selective for the phencyclidine binding site on the NMDA receptor (Wong et al. 1988). Gray et al. note the evidence that dopamine itself acts as a functional antagonist of the EAA system, reducing EAA release (e.g., Cheramy et al. 1986). Neuroleptics appear to have the reverse effect, increasing EAA release (for a review: Kornhuber & Kornhuber 1986).

It thus appears that there is an increasingly strong case for the inclusion of sigma and EAA systems in a model of schizophrenia based upon dopaminergic hyperactivity, abnormalities in cognition, and the links between the cortical, septohippocampal, and basal ganglia systems.

Schizophrenia and attention: In and out of context

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The authors of the target article are to be complimented on their bold efforts to provide an integrative theory of the positive symptoms of schizophrenia based on behavioral, pharmacological, and neurophysiological data. The success of such an endeavor rests on a detailed analysis and description of the behaviors to be explained, in this case the positive symptoms of schizophrenia, and a thorough understanding of each data domain and the interrelationships between the data domains themselves, particularly the to-be-explained target behaviors. These interrelationships are the basis of the theory.

One aspect of Gray et al.'s theory, then, concerns the interface between the positive symptoms of schizophrenia and data from behavioral paradigms (latent inhibition, blocking, and the partial reinforcement extinction effect) which assess the consequences of dopamine agonist/antagonist administrations. The basic tenet which relates these two domains, although not stated explicitly, is simply this: The normal attentional process(es) that governs these behaviors in animals and humans are identical to those that are disrupted in schizophrenia. Indeed, this theoretical statement has been made explicit by others, particularly in regard to latent inhibition (LI) (e.g., Lubow 1989; Lubow et al. 1982). The evidence supporting this contention is summarized in the target article (see also Lubow 1989 and Weiner 1990). If one accepts this congruence, then it follows that these behavioral paradigms provide powerful tools for developing a theory of schizophrenia. For example, if one maintains some version of a dopamine theory of schizophrenia, then manipulations within the behavioral paradigm should interact with the effects of dopamine agonist/antagonist administrations to mimic prespecified symptoms of schizophrenia. Since many of these behavioral paradigms have been extensively studied, one has the advantage of starting with a defined empirical base, which describes the conditions that influence the level of the effect.

This tactic has been used to explore the attentional deficit in schizophrenia, and it has suggested a specific mechanism whereby the attenuation of LI in acute, nonmedicated schizophrenics (Baruch et al. 1988a; Lubow et al. 1987) and "psychotic-prone" normal subjects (Baruch et al. 1988b; Lubow et al., submitted) can be explained from an analysis of the normal effects of context manipulations on LI.

To begin with, five empirical relationships between context manipulations and LI were identified (Lubow 1989).

1. A change in context from preexposure to acquisition-test reduces LI (e.g., Lubow et al. 1976).

2. For context and stimulus preexposure to be effective in producing LI, the two have to be preexposed conjointly (e.g., Hall & Channell 1986).

3. Context extinction following stimulus preexposure in that same context has little or no affect on the amount of LI (e.g., Baker & Mercier 1982; Hall & Minor 1984).

4. Context preexposure by itself, prior to acquisition, however, does interfere with subsequent context-CS associations or context-US associations (e.g., Balaz et al. 1982; Mowrer 1987), thus demonstrating LI of these context associations.

5. Context preexposure prior to stimulus preexposure in the same context increases the magnitude of LI (Hall & Channell 1985b).

Now, in addition to the basic premise that the normal attentional process(es) that govern LI in animals and humans are identical to those that are dysfunctional in schizophrenia, there is a set of facts describing the way context manipulations modulate LI. A theory that explains these facts provides insights into the dysfunctional attentional process in schizophrenia. According to one such theory (Lubow 1989), the subject, during preexposure, develops an associative link between the preexposed stimulus and its context, so that context becomes an occasion setter for the expression of the stimulus-no consequence relationship (Bouton & Swartzentruber 1986; Puente et al. 1988). It is the exceptional characteristics of occasion setters that allow one to understand the various effects of context manipulations on LI. In particular, (1) occasion-setting stimuli gain control of the behavioral expression of associations, and (2) occasion setters do not lose this ability when they are later presented repeatedly by themselves, that is, they do not exhibit typical extinction (Rescorla 1985; 1986).

Normal LI, then, develops as a result of conjoint stimulus-context preexposure, whereby context develops occasion-setting properties for the stimulus-no consequence association. As an occasion setter during the test phase, context prevents the previously exposed stimulus from being primed into short-term memory. The latter point, important for relating the context-LI data to schizophrenia, is speculative. Nevertheless, a number of considerations support this hypothesis (see Lubow 1989): Normal subjects preexposed to a stimulus under masking conditions, diverting subjects' attention from the to-be-target stimulus and necessary for producing LI in adults do not report awareness of that stimulus (Ginton et al. 1975). Since conscious perception of a stimulus is an accompaniment of its presence in STM, these data suggest that, at time of test, the preexposed stimulus does not reside in STM.

Indeed, common sense would seem to demand that unimportant stimuli (ones followed by no consequence) should be kept from STM, which because of its limited capacity can ill afford to be constantly disturbed by ecologically trivial events. A major problem, then, concerns how to keep these insignificant stimuli out of STM. It is proposed that the context, acting as an occasion setter, serves to minimize the amount of previously insignificant information deployed in STM.

Such a view has direct implications for schizophrenia. The fact that acute schizophrenics exhibit an absence of LI (Baruch et al. 1988a), resulting from better test performance of the stimulus preexposed group, can be attributed to a breakdown of the ability of the context to serve as an occasion setter for the expression of the stimulus-no consequence relation, the result of which is that STM is inundated with experimentally familiar but phenomenally novel stimuli. Frith (1979) has described the endproduct of this collapse in similar terms, referring to the inability of schizophrenics to limit the contents of consciousness. Similarly, Pogue-Geile and Oltmanns (1980) suggest that their schizophrenic subjects suffer from a reduction in "overall capacity to handle information in STM," and Rochester (1978) notes that such subjects may have difficulty in continuously accessing STM during conversation. These proposals, the data on which they are based, and many of the behaviors commonly agreed to be positive symptoms of schizophrenia, are all congruent with the notion that STM is "preoccupied" with irrelevant stimuli. The proposal put forth here is simply that these effects occur because of the absence of the normal occasion setting properties of context, which function to limit access of irrelevant stimuli to STM.

In regard to the target article, the message is two-fold. (1) A comprehensive theory of schizophrenia should place at least as much emphasis on behavioral as on neurophysiological data, particularly in the early stages of theory construction. (2) Such a theory, particularly if it uses attentional constructs based on LI in animals and humans, must account for context effects and relate them to the symptoms of schizophrenia.

Approximations to a neuropsychological model of schizophrenia

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Gray et al.'s model of the pathogenesis of schizophrenia is a noteworthy attempt to specify, in a far more detailed and precise manner than its predecessors, the anatomical, neural, and psychopathological relationships in the disorder. There is much merit in the proposal, especially because prior excursions in this area have been customarily reductionistic, often more constrained by the dopamine hypothesis, and generally clinically simplistic. The present model deserves attention on several grounds. It organizes considerable knowledge about schizophrenia, it is falsifiable, and hence it generates numerous testable predictions.

It is not without problems, however. It has two clinical shortcomings. First, its focus on certain of the positive symptoms associated with the illness impairs its specificity to schizophrenia. Not only are positive symptoms present in the active phase of acute schizophrenia, they are also characteristic of a variety of other psychoses, including mania and drug-induced psychosis. Given that their presence in different disorders suggests that they have a nonspecific etiology, undue dependence on them as the key to identifying the pathology of schizophrenia seems to carry some risk of error.

Second, the clinical presentation of schizophrenic illness is rarely free of so-called negative or deficit symptoms; the model is vague about this, but Gray et al. suggest that such negative symptoms as poverty of speech and social withdrawal might represent coping adaptations to minimize the effects of cognitive impairment. For several reasons this is not persuasive. The coping hypothesis requires in principle that there be evidence that positive symptoms reliably precede the appearance of negative symptoms; coping, in other words, does not occur until there is something to cope with. No such evidence is presented here. On the contrary, there is evidence that negative symptoms precede the temporal occurrence of psychosis or cognitive change. Paradoxically, it is of interest to note that the coping explanation was adduced to explain positive symptoms decades ago, as with Freud on delusions and the double-bind theorists on bizarreness in language expression. It also seems implausible that the specific negative symptom of impoverished content of speech and thinking (i.e., where the quantity of speech may be normal but little information is conveyed) represents a coping strategy.

A fundamental problem with the use of symptom categories as broad as those subsumed under the classic headings of positive and negative is that these categories lump together behaviors that, on close inspection, may be quite different in their measureable properties. Thus, an utterance may be rated as exhibiting poverty of content because it is repetitious, because it consists of partial sentences only, or for other reasons, all of

which have only the common attribute that they produce no coherent content. Nonetheless, the underlying pathologies may be quite different – a fact that is not discernible when only gross rating categories are used. In brief, current symptom categories need finer-grained analysis of the behavior that they imply if we are to use them to identify highly specific neuropsychological substrates.

In an earlier study (Manschreck et al. 1982), for example, we reported that abnormal voluntary motor movements were associated with formal thought disorder, affective blunting, and nonlocalizing signs of neurological dysfunction. These features were not associated with delusions or hallucinations, however. These observations seem inconsistent with the notion that certain negative symptoms represent an adaptation.

A related and fundamental issue is the set of problems that the heterogeneity of schizophrenia poses for any model of this scope. For example, we do not know whether schizophrenia is one or many disorders. Even without this knowledge our field is unable to define rigorously the essential characteristics of the schizophrenic condition. Although the etiology of schizophrenia need not be entirely specified in the model, it does seem to us that so fundamental an issue as whether the illness is a degenerative or fixed disorder (about which matters are not settled) certainly cannot be ignored. Given this lack of valid criteria for the diagnosis, any proposal for a neuropsychology of schizophrenia seems too ambitious and likely to fail.

It has struck us in our study of schizophrenia (whatever that may ultimately prove to be) how formidable are the tasks of defining the illness/es through reliable, quantitative laboratory assessment rather than through exclusive reliance on clinical judgment (e.g., Maher 1983). Instead of easing the task of identification, however, the latter approach may have obscured the complexity of the illness. For example, we must now be able to accommodate the finding of abnormal voluntary and involuntary movements in patients diagnosed with schizophrenia, ventricular enlargement among a subset of such patients, and among some patients major fluctuations and variations in the variety of speech anomalies, symptom patterns, and even prognoses. Indeed, variability in a host of features, including symptoms, arousal patterns, response to treatment, and so forth, appears to be a fundamental characteristic of the illness. Gray et al.'s model does not stand or fall on such considerations. Such models as this have the heuristic value of stimulating research. Ultimately, scientific investigation will test its use. We must sound a note of caution, however, and underline the need for midrange theorizing in schizophrenia. Specifically, we suggest more focused model building in neuropsychology. An example might be the pathogenesis of memory impairments or of disturbed speech and movements in schizophrenia. With effort, these more focused models may lead to a more comprehensive framework for understanding the disorder. In the meantime, we applaud the present attempt.

Neuropsychological vulnerability or episode factors in schizophrenia?

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The integration of cognitive and neural aspects of schizophrenia is critical to more comprehensive models of this complex disorder. The model proposed by Gray et al. is a very scholarly, thoughtful, and detailed attempt to bring available cognitive, neurochemical, and neuroanatomical evidence to bear on one aspect of schizophrenia, namely, the positive symptoms of the acute phase. The deliberate focus on the positive symptoms of the acute phase allows more specific components and linkages in the model, but it also leads to several conceptual and empirical dilemmas.

The primary dilemma is that the critical neuropathology on which the model is based is stable rather than transient in nature, but the positive symptoms of schizophrenia are often episodic rather than continuous. Similarly, this neuropathology presumably develops very early in life, whereas the first positive symptoms of schizophrenia typically do not occur until late adolescence or early adulthood. Thus, one is faced with the need to reconcile "good evidence both of neuronal loss and of abnormalities of neuronal morphology and packaging in several regions of the temporal lobe" (sect. 3, para. 7), specifically hypothesized damage to the subiculo-accumbens pathway, on the one hand, with the delayed onset and variable course of the positive symptoms, on the other. The influence of dopamine-blocking medication helps to explain the typical remission of positive symptoms with treatment of acute episodes, but it fails to account for the initial onset of positive symptoms or the variable course of positive symptoms during drug-free periods. The model, therefore, does not adequately explain how such temporal disparities arise.

A very relevant distinction here is the difference between factors associated with *vulnerability* to schizophrenia and those associated with *episodes* of positive symptoms (Cromwell & Spaulding 1978; Nuechterlein & Dawson 1984a; Zubin & Spring 1977), with the former abnormalities being continuously present and the latter present only during episodes. From this perspective, the neuropathology of the subiculo-accumbens pathway would be considered a vulnerability factor for the development of positive symptom episodes. Additional factors would be necessary to account for the triggering of such episodes.

A related issue is that the time course of the core cognitive dysfunctions in schizophrenia posited by the Gray et al. model is not clearly connected to the proposed neuropathology. Are the cognitive anomalies, specifically the weakened influence on current perception from stored memories of past regularities in perceptual input, present only during periods of positive symptoms or are they continuously present to some degree? The focus on a contrast between acute and chronic schizophrenic patients highlights such aspects of cognitive functioning as latent inhibition that become abnormal only during episodes of positive symptoms. The view that failure to show latent inhibition is linked in time to symptomatic periods in schizophrenia is strengthened by a closer examination of the Baruch et al. (1988) study. Disruption of latent inhibition was found to be the result of *significantly* enhanced learning in the preexposed, symptomatic group only if the schizophrenic patients were divided into those with the highest versus lowest total pathology scores on the Brief Psychiatric Rating Scale, although a similar but nonsignificant tendency was present for the contrast between acute schizophrenic and chronic schizophrenic patients. Thus, a high level of current symptoms is linked to enhanced learning in the preexposed schizophrenic group and failure to show latent inhibition, whereas schizophrenic patients with low levels of current symptoms show normal latent inhibition. Changes over time in a cognitive dysfunction closely associated with changes in positive symptoms do strengthen Gray et al.'s hypothesis that the cognitive dysfunction may be linked to the positive symptoms of schizophrenia. If these episode-linked cognitive deficits are the immediate mediating factors in positive symptom development, however, what triggers the onset of these cognitive deficits, given that the proposed neuropathology has a more stable character?

Perhaps the authors would suggest that dopamine hyperactivity serves as the mediating variable between the proposed stable neuropathology and the episode-linked cognitive dysfunctions. The time course for dopamine hyperactivity would then need explication. Furthermore, examination of the Baruch et al. (1988) study reveals that evidence for dopaminergic hyper-

activity as an intermediate variable rests on a very tenuous assumption. In most cases the acute schizophrenic patients were not only taking dopamine-blocking medications when tested, but their dosages tended to be higher than those of the chronic schizophrenic patients. Thus, unless Gray et al. posit a substantial delay in dopamine-blocking activity after drug administration, these acute schizophrenic patients may not have been hyperdopaminergic at the time of testing, as they assume. In schizophrenic subjects, the connection between current symptoms and disrupted latent inhibition appears to be much clearer at present than the connection between dopaminergic overactivity and disrupted latent inhibition. As Baruch et al. (1988) correctly note, direct measures of dopamine activity in schizophrenic patients are needed to establish the latter link.

One other issue regarding temporal aspects of the model deserves comment. The authors' presentation of cognitive dysfunction in schizophrenia might lead the reader to assume that cognitive abnormalities are limited to acute symptomatic periods. On the contrary, a substantial body of evidence now indicates that some information-processing dysfunctions are present during periods of clinical remission in schizophrenic patients, as well as among first-degree relatives of schizophrenic patients (Asarnow et al., in press; Holzman 1987; Nuechterlein, in press; Nuechterlein & Dawson 1984b). These cognitive dysfunctions are hypothesized to be linked to vulnerability to schizophrenia, rather than to periods of active schizophrenic symptoms. Such relatively enduring cognitive dysfunctions are temporally well-matched to a static underlying neuropathology.

Given these temporal considerations, a comprehensive model of schizophrenia would need to explain a combination of enduring cognitive dysfunctions and episode-linked cognitive dysfunctions. Gray et al. suggest that their model is consistent with the view of Frith (1979) that schizophrenia arises from a disruption in automatic processing. A possibility noted by Nuechterlein and Dawson (1984b) is that such a disruption in automatic processing occurs only during acute positive symptom periods, whereas other limitations affect controlled information processing at high processing loads during periods of remission. Such multiple-process formulations may be necessary to account for the diverse temporal patterns of cognitive dysfunctions in schizophrenia.

Gray et al. are to be commended for their creative and ambitious efforts to provide a cross-sectional model of positive symptoms that integrates cognitive, neurochemical, and neuroanatomical aspects. We would encourage them to incorporate more fully into their model the longitudinal perspectives regarding schizophrenia.

Bases for irrelevant information processing in schizophrenia: Room for manoeuvre

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The trend is to move away from the strong version of the dopamine (DA) hypothesis of schizophrenia. What better way than with Gray et al.'s suggestion that the subicular-accumbens pathway is where the impairment can be observed in positive schizophrenia (PS)? They incorporate current evidence of temporal lobe dysfunction (the frontal lobe is largely put to one side), yet still allow for the partial therapeutic effect of D2 antagonism in those with PS. Is this reasonable?

A weakness of Hemsley's, Frith's, and Gray's formulation of the psychological processes underlying PS is the overuse of dichotomies (Occam's Razor) to solve a heterogeneous problem. The PS problem is identified in terms of errors of willed-intention versus stimulus processing (Frith), response versus stimulus set (Hemsley), controlled versus automatic processing (Gray and others). A look at the range of event-related potentials recorded in discrimination tasks with attentional demands and the variables affecting them suggests that such dichotomies may be oversimplifications of the processes under discussion (Hackley et al. 1978; Hillyard et al. 1978).

Yet the postulate that more processing capacity is allocated to irrelevant stimuli is "congruent" with the common view that PS subjects are more distractible and thus have fewer resources for processing relevant stimuli. Direct support comes from a recent ERP study of P3a versus P3b in schizophrenics on a 3-tone oddball task (Grillon et al. 1990). [See also Naatanen: "The Role of Attention in Auditory Information Processing as Revealed by Event-related Potentials and Other Brain Measures of Cognitive Function" *BBS* 13(2)1990.] The N2 and related mismatch negativity component (MMN) as indicators of stimulus evaluation and stimulus mismatch have been less frequently studied in PS. N2 latencies are longer in schizophrenics (Brecher et al. 1987; Grillon et al. 1990). In our current work with a 3-tone oddball task, the MMN (derived as rare – standard ERP) develops over 240–280 msec in controls. A comparable frontal negativity develops in PS subjects 110 msec later (if at all), when posteriorly an (abnormal) P3 is already showing. This is supportive of Hemsley's "weakening of the influence of stored representations on perception" and is logically compatible with a monitoring problem (Frith).

Gray et al. rightly attach importance to the schizophrenic who "can see the details but has difficulty to extract the meaning." Schizophrenics have difficulty in seeing the wood for the trees, the figure for the tachistoscopically presented dashes of Schwartz-Gilmore & Place (1980; Wells & Levanthal 1984). Reviewing this work, Straube & Oades (1991) note that this problem is not restricted to PS subjects. Furthermore, gestalt perception is not a controlled process (Robertson 1986) – the type of processing Gray and others suggest is impaired in PS. One could argue that many schizophrenics show impaired information processing 10–80 msec after its receipt, where many authors would have difficulty saying that processing was controlled (e.g., critical stimulus duration and transient channels in masking studies, Balogh & Merritt 1989; Saccuzzo & Braff 1981, and prepulse inhibition, Baker et al. 1990). Gray et al. could rightly object, however, that although these findings relate to subjects with schizophrenia-like symptoms, their target group (PS) has not been appropriately studied. As selective attention seems capable of altering processing at this early stage, however (e.g., Hackley et al. 1987), we propose that the schizophrenic deficit in information processing is better termed concept-driven. The difference here is that controlled processing of a set of events leads to changes that affect the processing of *future* events.

Schizophrenic processing is usually impaired when there is no clear stimulus-response contingency. In interpreting a proverb, schizophrenics often "select" individual words/stimuli and make associations with these independent of the context. When the subject must take account of the context of "A," the response is concept-driven. An example of such a task is an "if-then" situation (if stimulus "A" on "B" then do "X," but if "A" on "C" then do "Y"). Animals can rapidly learn such contingencies *unless the hippocampus is damaged* (Sutherland et al. 1989). Such tasks require an ability to store stimulus configurations and to match new ones to them. This ability is fundamental in generating appropriate responses during conversation (Hemsley), monitoring the goal of a speech plan (Frith), and it recalls Gray et al.'s suggestion that "the integration of stored information . . . for perceptual control is the site of the impairment."

Gray et al. focus very narrowly on the subiculum and its input to the accumbens. It is not clear whether input over the *entorhinalis* is important to their scheme. Here anatomical anomalies have recently been reported (Beckmann 1991; Falkai et al. 1988b). Do they include the *presubiculum*? From here

efferents pass to the entorhinalis and prefrontal cortex, where hypofrontal activity by various measures may not just reflect chronic or negative symptoms (Weinberger 1987) but even symptom state (Hawton et al. 1990). Do Gray et al. wish to subsume the function of these areas in their hypothesis? Can they explain why precommissural fibers from the subiculum to the accumbens *and* septum but not postcommissural fibers to the hypothalamus should be so susceptible to hippocampal or cholecystokinin (CCK) dysfunction (the role of the hypothalamus in PS has not been widely discussed)?

The *septum* is conspicuously absent from the argument. It receives a marked VTA-DA input (and input using most known transmitters besides) and, like the entorhinalis, is crucially placed to gate input to the hippocampus. This is particularly important in view of a putative DA role in switching referred to by Gray and myself (sect. 7, para. 2). But "congruent" with their hypothesis is the coincidence of the frequent age of first showing schizophrenic symptoms (16–20) and normal myelination processes in the subiculum (Benes 1989).

Gray et al. have been searching for a way to link DA activity to temporal lobe pathology in a theory of PS. By analogy with nigral-DA and its protective role in epilepsy, I suggest a VTA-DA role in the septal and entorhinal hippocampal-gates protecting against PS/information processing dysfunction. [My analogy takes into account the anticonvulsant effects of DA agonism (Loescher & Czuczwar 1986), decreased ascending DA activity associated with decreases of seizure thresholds (Turski et al. 1990), higher temporal lobe DA activity (Louw et al. 1989), changed subcortical D2 binding (Csernansky et al. 1985) associated with seizure foci, and protective effects of pars reticulata stimulation (Sabatino et al. 1988)].

Gray et al. note, if we overlook details (sect. 3, last para.), that DA utilization or D2 binding increases 28d after hippocampal surgery in the rat. They ask whether damage to subicular input can produce a functional impairment that is reversed by neuroleptics. They may recall that the report of Oades & Isaacson (1978) supports this prediction. Rats learned over 11 10-trial sessions to find 4 food pellets placed in the same 4 holes of a 16-hole board without visiting nonfood holes. They visited holes in an individually specific sequence on 8/10 trials. A preferred sequence did not develop in animals with hippocampal damage (H) or those treated with haloperidol. However, haloperidol treatment, from session 4, reduced errors by 28% in H animals (7–8% in saline/drug lesion/sham controls). On withdrawal of haloperidol (2-day pause before retest), the H group made 30 errors, whereas controls made 3–5 more errors on average. A similar *partial* normalization of performance or symptoms is often reported for PS subjects who respond to neuroleptics.

The bias of Gray et al.'s review of neurobiological studies with latent inhibition (LI) or conditioned blocking (CB) is a bit misleading. Let me briefly take some reports at face value, although I have no room here to discuss their strengths and weaknesses.

The report that amphetamine in the accumbens of the rat disrupts LI (Solomon & Staton 1982) certainly supports Gray et al. D2 supersensitivity disrupts LI (Crider et al. 1986), apparently reconciling the effects of increased DA utilization and D2 binding. But this supersensitivity was generated by chronic haloperidol treatment that renders other projection regions supersensitive. Indeed, this group (Kamer et al. 1981) dissected the septum out along with the accumbens. The septum, septal DA, and septal opiate receptors are not without various effects in this paradigm (Burton & Toga 1982; Gallagher et al. 1987; Oades et al. 1985). In addition, damage to the mamillary bodies and ventral hippocampus, but not to the dorsomedial thalamus or dorsal hippocampus, can attenuate CB (Rickert et al. 1981). This study, and also Garrud et al. (1984), show that hippocampal damage does not interfere with LI or CB in everyone's hands, despite contrary reports (Nicolle et al. 1989). Although Gray et al. do report on serotonin studies, they are too dismissive of the complexities of the effects of noradrenergic manipulations on LI and CB (e.g., Caza 1984; Mohammed et al. 1986; Rickert & Lorden 1989).

Oades et al. (1987) reported on the effect of 6-OHDA lesions in the PRF and septum on CB. Depletion of septal DA and DOPAC (decreased DA use or changed DA/NA ratios) was associated with the eventual facilitation of CB (latency of response to redundant information); impaired CB after PRF treatment seemed to depend on coincidental decrease of DA in the septum (increased use). Both manipulations were without effect on NA, DA, and DOPAC in the accumbens and striatum. This argues against too narrow a focus on the n. accumbens in the hypothesis of Gray et al.

Gray et al.'s account of disrupted LI in PS subjects remains equivocal when these showed more symptoms and severe ones than the chronic patients; the groups were also not matched for medication. Currently in Essen we are comparing the CB performance of schizophrenics, neurotics, and healthy controls with their urinary monoamine excretion. A large range of values for DA excretion in schizophrenics (usually $\leq$ to controls) reflects symptom and treatment differences and varies as a hyperbolic function with the expression of blocking. A similar relationship in controls is restricted to a far narrower range of values for both DA and blocking. At a general level the implication supports the argument of Gray et al. that the type of information processing measured by this paradigm is influenced by DA activity. Its locus and specificity to PS has not yet been demonstrated, however.

In conclusion, yes, Gray et al.'s hypothesis is reasonable, but some manoeuvres are needed to accommodate the results of others.

Is another loop needed to explain schizophrenia?

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It would seem that there is now no lack of theoretical models of schizophrenia – lately, one has appeared every year or so. Each presentation adds some unexpected new twist to our gropings for insight into the complex psychopathology of schizophrenia. The Gray, Feldon, Rawlins, Hemsley & Smith target article is of this nature. It provides some intriguing new ideas and poses several important questions.

One of the first commendations one can make of Gray et al.'s article concerns its practicality. The authors state clearly that their model deals primarily with acute schizophrenia (Type I) and the so-called positive symptoms rather than the chronic state (Type II). The Gray et al. model has not been weakened by attempting to "stretch" its conclusions to incorporate both acute and chronic states.

Another major asset of the model is that it places emphasis on the role of inadequate interactions between stored experience and current perception as a primary causal factor in thought disorder and other positive symptoms of schizophrenia. This is a satisfying biological construct because it is congruent with views of clinicians who see schizophrenic patients' failure to profit from or use stored experience. It may be, however, that the schizophrenic disturbance is coupled with information-processing deficits (e.g., Braff & Saccuzzo 1985; Freedman et al. 1987; Geyer & Braff 1987). Such deficits would be identified with brain circuitry other than that involved in the Gray et al. model.

Gray et al. have presented a model in which units of motor programs (termed motor steps) become temporally interwoven into a sequential pattern of behavior directed toward a specific goal. Judgments as to the selection of appropriate motor steps are shouldered by circuitries outside of the motor programs

themselves. That is, neural circuits involving the dorsal striatum and/or lateral thalamic nuclei (feedback loops I and II) contain the required motor steps. Another circuit incorporating the nucleus accumbens "plans" judicious switching of steps for the smooth transition of final motor programs. Consultation for this processing is offered to the accumbens from two sources: the amygdala, which has knowledge of previously experienced reinforcement contingencies, and the septohippocampal system, which appraises each motor step as to whether or not it will achieve the expected outcome. Termination of inappropriate motor steps is actuated by the influence of accumbens on the ventral tegmental dopamine system, with its putative inhibitory action on Spiny I neurons. Reselection processes are a little less clear but involve accumbens efferents to the dorsomedial thalamus and subsequent relays to prefrontal cortex.

According to the model, the above description mirrors the brain's protocol for an appropriate execution of a spoken sentence. As indicated by the authors (sect. 9, para. 1), a spoken word could be conceived of as a motor step, the machinery for which is contained somewhere within the caudate motor system. Linking words into meaningful communication would incorporate the orderly guidance functions of the accumbens system that switches into and out of motor steps as is necessary to create desired syntax. Language production, like all goal-directed behaviors, requires harmonious communication between caudate and accumbens motor systems. It is this interaction that we would like to address. Does current empirical information support the notion that an accumbens-related circuit intervenes in the dorsal striatal-dorsal pallido-thalamo-cortico-dorsal striatal network to switch ongoing processing or are there more parsimonious possibilities?

Investigations of localized brain lesions (Luria 1977; Riklan & Cooper 1975; Van Buren 1975) and, more recently, studies of electrical stimulation under local anesthesia (Ojemann 1983), have identified sets and subsets of motor programs in the lateral thalamus of the dominant hemisphere that serve singular phases of language production. From the ventroanterior nucleus, passing through the medio-central core of the ventrolateral nucleus and ending in the anterior superior pulvinar, discrete areas have been found that, when electrically stimulated, evoke the following dysfunctions: (a) disruption of intended movements of the orofacial musculature; (b) arrest of the expiratory side of the breathing cycle; (c) inability to name an object correctly (e.g., "balloon" for "arm," Ojemann & Ward 1971); (f) perseveration of the first syllable of a word during a period of stimulation – the word to be completed only when stimulation terminates; and (e) forced insertion of a sensible word or phrase.

Evoked speech may or may not remain constant with repeated stimulations of the same site. For example, initial stimulation of one such site evoked the response, "Left is at my side," yet a second produced, "Professor, I know exactly what people are talking about me" (Schaltenbrand 1975). Other subjects produced such unlikely words or phrases as "ace," "twinkie," "that's goofy," "shucks, once in a while" (Ojemann 1975). Stimulation-induced spontaneous speech has so far been found to be localized exclusively within the thalamus. The sites for language disturbances mentioned above also have homotopic neocortical areas usually considered to subserve language functions. Within the cortical regions of the inferior frontal operculum (Broca's area), the supplementary motor area, and the parietal temporal junction (Wernicke's area), however, no spontaneous language has been evoked with stimulation (Ojemann 1976).

The body of evidence discussed above supports the notion that the lateral tier of the dominant thalamus contains circuitry for motor programs that can initiate the basic mechanics of articulation (i.e., control of orofacial musculature and expiratory cycle), aid in word search, and direct whole syntactic units into final motor pathways. Gray et al.'s model requires the intervention of an accumbens influence somewhere within the ordered sequential processing encountered in the thalamus. The stimulation studies show that thalamic language production areas are topographically confined to regions lateral to the internal medullary lamina. Accumbens projections to the thalamus are restricted to areas medial to the internal medullary lamina (i.e., the dorsomedial nucleus). Because these two regions have no known intrathalamic connections (Jones 1985), the only point of commonality, it seems to us, is the prefrontal cortex and its involvement with the frontal cortical language field.

The relationship between schizophrenia and inner speech has a rich heritage (Bleuler 1934; Johnson 1978; Parish 1897). More elaborate and formal treatises by Hoffman (1986) and Frith and Done (1988) have continued this tradition. They propose that unwilled, unmonitored, or unintended inner vocalizations are interpreted by the individual as alien and not self and, as such, are perceived as auditory hallucinations. Integration of these ideas with the growing recognition of the critical role played by thalamus in language production should not go unnoticed. Preliminary findings, as yet unreplicated, that the thalami in brains of schizophrenics have unusual levels of dopamine, add further significance to the above remarks (Oke & Adams 1987; Oke et al. 1988). Of course, the idea that excess thalamic dopamine or any other biochemical disturbance could produce the same effects as electrical stimulation and be linked to schizophrenic speech disorder remains as speculative as most model circuitry concepts.

A realistic model will be much more complex and will consider longitudinal neuropsychodevelopment

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Gray et al. correctly indicate that I have recently put forward a conceptual position similar to theirs (Patterson 1987). Nonetheless, there are some differences in emphasis that, if synthesized, may strengthen both positions. It is important to accept (at this stage of neuroscience/cognitive science convergence on schizophrenia) that much will be gained by crossing disciplinary boundaries and attempting to forge a more complex conceptual and mechanistic picture. In addition to my admiration for the work of each of the authors, I offer my respect for this latest heuristic addition to the literature. It is often said that an academic would rather use his colleague's toothbrush than use his terminology – I will try not to abide by this adage.

What is a clue and what is a red herring in schizophrenia research? The authors believe hallucinations to be a clue. I do not. Despite their colorful appearance in schizophrenic symptomatology, hallucinations may be epiphenomenological to the illness. They do not occur in all schizophrenics and they *do* appear in such other conditions as alcoholism. Data from the brainstem auditory evoke response (BSAER) are pertinent here. Begleiter et al. (1981) have shown that during the hallucinogenic phase of chronic alcoholism wave five (V) of the BSAER is diminished, only to normalize as detoxification proceeds and clinical recovery is attained. Swedish data (Lindstrom et al. 1987) indicate diminution of wave V in schizophrenics with hallucinations too, no such reduction being seen in schizophrenics without hallucinations. Bick and Kinsbourne (1987) have characterized hallucinations as a loss of the "tag" that denotes stimulation of internal/external origin. As this internal/external locus is of very primitive origin, it should be operational both early in the information processing chain and low down in the brain. Occurring approximately 6 msec from stimulus onset, wave V seems to satisfy both criteria. It might therefore be proposed that the functioning of the neurological apparatus subtending wave V represents the "bit" setting that

corresponds to the perceived internal/external locus of stimulation. I differ most from Gray et al. in emphasizing the "assembly" of information in the milliseconds from physiological transducer activation to the activation of appropriate cortical columnar structures. Implicit in this emphasis is the hypothesis that because perception is a learned process, activation of appropriate aspects of prior experience must take place in parallel with current stimulus input to correctly "assemble" information.

In my formulation, each instant of experience is neurologically encoded as an enlarging upward barrage of nerve pulses, progressively added to by each successive brain structure, with the most significant "bits" being added by the limbic apparatus in tight interaction with the striatum and cortical columns. In this construction each instant of experience has subcortical "content addressability" (see Pay 1981) for cortical relay, which, over time and experiential repetition, comes to blast a particular "pulse coherence demodulation" into particular cortical columns. In this way the individual brain becomes structurally and functionally identified with a particular life experience.

I am in complete agreement with Gray et al. when it comes to the importance of subcortical structures, and we all appear persuaded by data from Bogerts et al. (1985), Jakob & Beckmann (1986), and Conrad & Scheibel (1987) (to name but a few), which indicate variable subcortical pathology in schizophrenia, possibly of neurodevelopmental origin. If this is really the case (and it remains to be demonstrated), then its importance to me is that the affectively vectored reactivation of pertinent aspects of prior experience may be defective. In my opinion, the limbic brain assembles the most significant "bits" that are contributed to each and every instant of experience; in schizophrenia, these are either defective, missing, or inconsistently contributed. The end result is that in later (postchildhood) life the affectively vectored automaticity of reconstruction/retrieval from previous experience is not achieved, resulting in the *inappropriateness* of schizophrenic behavior.

This is the best I can come up with at present to account for schizophrenic behavior's escape from the contextual constraint that so powerfully controls the behavior of normal subjects. This is empirically testable with paradigms manipulating contextually generated expectancy, with concurrent measurement of brain events in the millisecond time epoch. Evoked potential waveforms in the 100 msec epoch need to be further explored in schizophrenia (Patterson et al. 1987), in addition to such waveforms as the N400 produced by contextually generated expectancy failure in linguistic paradigms.

I am somewhat surprised that Gray et al.'s exploration of language functioning in schizophrenia has not included Crosson (1984) or Crosson & Hughes (1987). Many of the brain structures implicated by Gray et al. are also implicated by Crosson. Hence the importance of possible defects in the globus pallidus (direct evidence by Early et al. 1987) or the thalamus (post mortem evidence from Oke & Adams 1987), or the growing importance of parietal structures in complex cognitive processes, has not been given much weight. I also find it regrettable that the complex neuromodelling of Pay (1980a; 1980b; 1981; 1982) was not also incorporated into the proposed neuromodel. One is left with the impression that the model, having once been proposed for anxiety states, could be adequately "cobbled" to do duty for schizophrenia. In my opinion, it needs to be expanded greatly beyond its present form, although I heartily appreciate the incorporation of the whole scheme of "state dependence." I am also unsure how much is gained by relying on such clinical (epi?)phenomena as acuity/chronicity or positive/negative symptoms. Longitudinal studies show such variability within the symptom picture of each patient over time that clinical (rather than more "biological") markers may not produce a fruitful subclassification for elucidating the pathogenesis of the disorder. The leap from "symptoms" to neural mechanisms may be too great. A far more profitable strategy may be to use the tightly defined, time delimited, information processing stages as described by cognitive scientists as the "behavior" to which realistic neural controlling mechanisms may be fitted.

NOTE

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Why don't preschizophrenic children have delusions and hallucinations?

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In the past decade, neuropathological, and neuroimaging studies have provided indisputable evidence that a proportion of cases of schizophrenia have structural brain abnormalities. The theories of schizophrenia that have arisen from these studies have been firmly rooted in the Kraepelinian disease model (Murray et al. 1988; Weinberger 1987), and psychologists have contributed little to them. As a result, although our knowledge of the basic brain abnormalities has been greatly enhanced, our understanding of the mental mechanisms involved has not. Gray and his colleagues make a heroic attempt to bridge the brainless hypotheses of behavioural psychology and the mindless theories of biological psychiatry. But is it a bridge too far?

Gray et al.'s emphasis is firmly placed on the neuropathological abnormalities in the temporal lobe as the origin of the positive symptoms in schizophrenia. This has great theoretical appeal (Trimble 1990) but there is as yet little direct evidence linking the two. For example, two groups (Altschuler et al. 1987; Jakob & Beckmann 1986) have claimed that cytoarchitectonic abnormalities are characteristic of more severe schizophrenia, but they do not specifically point to an association with positive symptoms. In fact, most evidence concerns the nonspecific finding of increased cerebral ventricular size and relates it to the negative syndrome (Crow 1985). Furthermore, a number of studies (e.g., Bruton et al. 1990; Weinberger et al. 1980) have reported that such structural changes as enlarged ventricles and decreased brain weight are associated with the abnormalities of cognition, personality, and social functioning in childhood that are found in some preschizophrenics and that we consider to represent the precursors of the adult negative syndrome (Murray et al. 1988).

This is consistent with the evidence that the structural abnormalities are developmental in origin. First, the heterotopic prealpha cells that have been reported in the parahippocampal gyrus imply a failure of neuronal migration during foetal life. Second, gliosis is unusual in schizophrenia, and yet this is the normal reaction of the brain to injury or inflammation in all but the first few months of life. Third, many studies have reported that the enlarged cerebral ventricles found on CT and MRI scans in a proportion of schizophrenics are associated with a history of obstetric complications (Lewis et al. 1989).

It seems plausible then that many features of the negative syndrome arise in childhood out of neurodevelopmental impairment. But why should such an early neural dysfunction not produce the false beliefs and perceptions characteristic of the positive syndrome until nearly two decades later? Developmental psychologists, investigating the way the cognitive competence of young adults differs from that of pre-adolescents, point particularly to the greater capacity of the former to appreciate the relationship between correct and incorrect beliefs. For example, Chandler (1989) states that "not until adolescence do young persons begin to understand that divergent views are . . . a function of all beliefs being inescapably relative to the framework of the entire knowledge construction enterprise."

This statement reminds one of the information processing functions that Gray and his colleagues attribute to the septohippocampal system and their claim that it uses information from stored memories to make comparisons between the predicted and actual state of the world.

Could a pre-existing lesion lie dormant until it was unmasked during adolescence by maturational changes designed to enable the hippocampal formation to undertake properly its adult comparator functions? Perhaps the postulated "failure to integrate current contextual information with stored information relevant to such contexts" could become manifest in delusions and hallucinations. It is therefore of interest that Benes (1989) has recently shown strikingly increased myelination of the subicular and presubicular regions during the late adolescent period in normal brains. She notes the importance of this region, which Gray et al. regard as the "heart of the comparator function" in normal cortico-limbic relays and suggests that myelination of key links in this circuitry may be "permissive" for the expression of a previously latent defect in schizophrenic brains.

Such a theory would not explain why there are such marked interindividual differences in the presentation of schizophrenic symptoms or why many patients show a relapsing and remitting course. Indeed, Gray et al. do not appear to appreciate the fragility of the whole concept of schizophrenia, especially when one considers that, in his later years, Kraepelin himself looked on the disorder as a merely a provisional category. Even today, some authorities regard all psychosis as a continuum, whilst others, including ourselves, believe that schizophrenia is itself heterogeneous. The view most compatible with recent neuroimaging studies is that the chronic form is associated with structural abnormalities and presents aspects of the negative syndrome from childhood; like other neurodevelopmental disorders, it is more common in males. [See also Gualtieri & Hicks: "An Immunoreactive Theory of Selective Male Affliction" *BBS* 8(3)1985.] In contrast, the relapsing and remitting form has an onset in adult life and is not accompanied by gross structural change; it is more common in females and may be closely related to manic depression (Castle & Murray 1991). Thus, a model purporting to explain the formation of positive symptoms, which occur in both acute and chronic forms, would need to have considerable plasticity to account for such aetiological diversity.

Gray et al. explain that their model is speculative, and as such it is highly imaginative and beautifully constructed, but even speculative buildings require firm foundations. Unfortunately, some of these are less secure than the authors appear to believe. For example, in attempting to establish a functional link between the temporal lobe abnormalities and the results of behavioural experiments, Gray et al. rely heavily on the dopamine hypothesis of schizophrenia. There is a paucity of direct evidence for this hypothesis, however, and many researchers find Wong et al.'s (1986) claim of increased receptor density in untreated schizophrenics less convincing than its refutation by Farde et al. (1990). In addition, there is continuing controversy over the postulated dopaminergic overactivity of projections to the nucleus accumbens because of loss of subicular glutamatergic input (Roberts et al. 1983). Gray et al.'s treatment of this conflicting evidence is illustrative of their recurrent tendency to cite a finding (for example the notion that CCK input to the subiculo-accumbens projection is excitatory), state the caveat (that CCK may not be excitatory to pyramidal neurones as it is co-localised with GABA inhibitory neurons), and then to sweep this caution aside. Furthermore, recent research shows much lower densities of CCK receptors in the human, as compared with the monkey and rat, hippocampal region (Kohler & Chan-Paley 1988).

A further difficulty concerns the narrowness of the experimental focus. It is true that models concerning motor activity in animals are useful in constructing models of psychiatric disorder, and Gray et al. make extensive use of these. Yet, in such models there is a risk of neglecting the cognitive activity that prompts motor behaviour or of concluding prematurely that these processes are mediated by the same brain regions. This is most clearly expressed in the authors' notion that their model of striatal and septohippocampal interactions allows them to treat cognitive abnormalities in acute schizophrenia as "a special kind of disorder in motor programming and monitoring."

In summary, Gray et al. suggest that schizophrenics suffer from "a weakening of the capacity to select for cognitive processing only those stimuli that, given past experience of similar contexts, are relevant." Some readers may conclude that the authors themselves suffer from a weakened capacity to distinguish between the relevant and irrelevant, and that this has caused them to develop a complex delusion regarding the brain mechanisms underlying schizophrenia. We do not share this view. The task of synthesising the disparate neuropathological, neurochemical, and psychological theories of schizophrenia *is* a daunting one. Gray and his colleagues have ventured where most of us fear to tread and can be forgiven for having developed a few overvalued ideas amongst very many productive and testable ones.

A heuristically useful but empirically weak neuropsychological model of schizophrenia

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The neuropsychological model of schizophrenia proposed by Gray et al. is an impressive, if somewhat prolix, speculative tour de force. Although their main idea of a basic limbic dysfunction is largely a refinement of previous hypotheses – not all of them acknowledged unfortunately (e.g., Matthysse 1980; Reynolds 1989; Schmajuk 1987) – the model is valuable because (1) it provides a heuristically useful approach to bridging the gap between neuropsychological studies of patients and animal models and (2) it strives for mechanistic specification and testability.

We feel that the model might have been closer to the mark, however, had the subicular dysfunction been proposed as a component of a neural disorder more pervasively affecting the coordination of widely distributed cortical-subcortical neuronal loops – widely distributed because a plethora of functions are deranged – as recently suggested by Cleghorn and Albert (1990). Both clinical observations and systematic studies (Cleghorn et al. 1990) lead us to agree with Gray et al. that the specific disorders of memory and will are important. Other neuropsychological features may be just as important, however, for example, slow reaction time, the lack of emotional colouring of experience and memory, and the greater impairment of recall ("forgetting to remember") than recognition (Goldberg et al. 1990). These impairments may contribute to the weakening of the influence of stored memories on current perceptions (Hemsley 1987a), but is one more salient than the other? We suspect, with others (Carpenter et al. 1990), that there are multiple deficits.

A large within-subject variability, always a problem for schizophrenia researchers, may in fact be a central feature of schizophrenia (Cleghorn & Albert 1990). It is difficult to see how the model of Gray et al. can account for such variability in measures of information processing, psychophysiological responses, psychological test performance, neuroendocrine responses to drug challenges, neurotransmitter metabolites in cerebrospinal fluid, and symptomatic response to treatment. Variability implies a lack of modulation of many functions, and the lack of synchrony of cognitive functions is an obvious feature of schizophrenia. Can Gray et al. argue that mechanisms under-

lying the impairment of conscious monitoring account for the lack of modulation of so many functions?

We think that the definition of the core neuropsychological features of schizophrenia is incomplete. A study of the specificity and sensitivity of measures of the neuropsychological features proposed by Gray et al. and by others is required to define the boundaries of a cognitively homogeneous group of schizophrenics, a necessary prerequisite for neural models of such specificity.

Turning to the details of the model, the struggle for internal coherence and empirical support is not always victorious, which is inevitable perhaps, given the ambitious scope of the enterprise. Here, we can only list some of the apparent difficulties:

(1) Springer & Isaacson's findings (1982) would indeed support the hypothesis that glutamatergic hypoactivity in the subicular-accumbens pathway produces the reported up-regulation of dopamine receptors in the accumbens of schizophrenics (Seeman et al. 1984). Such hypoactivity could not explain the reported up regulation of dopamine receptors in the dorsal striatum of schizophrenics, however (Seeman et al. 1984), because the subiculum does not innervate the dorsal striatum.

(2) Gray et al. obtained results discrepant from those of Springer and Isaacson (1982), which forces them to conclude that glutamatergic activity in the accumbens may decrease dopamine turnover and release, in contrast to cited data from Glowinski's lab. A further implication of their conclusion, also not supported by available data (Reynolds 1989), would be that striatal dopaminergic activity is increased in schizophrenia. The uncertainty about the glutamatergic-dopaminergic interactions in the accumbens clouds the model.

(3) An important component of the model is the suggestion that subicular and dopaminergic neurons discharge at the end of ongoing motor programs to inhibit them (sect. 9, para. 11; para. 6). Single unit studies of dopaminergic neurones, however, (Strecker & Jacobs 1987), do not support this contention. Furthermore, in keeping with a penchant to bite their own theoretical tails, Gray et al. first argue at length how subicular activation mediates inhibition of ongoing motor programs (sect. 9, para. 11), then they are forced to repudiate the argument because of contrary evidence (sect. 9, para. 13). What is the point of the exercise, then? The clouds get denser!

(4) Subicular activation is suggested to mediate both orientation to novel stimuli (sect. 9, para. 14; sect. 10, para. 2), and habituation (sect. 4, para. 8; sect. 10, para. 3), namely, to represent both mismatch and match signals. How is that possible? The clouds are now very dense!

(5) The model suggests that a subicular lesion produces disorders of motor programming but not motor stereotypies because the subiculum does not innervate the dorsal striatum. There are two problems here: First, it is not clear why motor stereotypies belong in a category different from disorders of motor programming. Second, the study by Owens et al. (1982), cited as supporting the prediction of a disorder in motor programming, actually describes a high prevalence of orofacial motor stereotypies and choreic dyskinesias in neuroleptic free schizophrenics, which is suggestive of dysfunction of the dorsal striatum.

(6) Subicular lesions would be expected to impair the functioning of all structures innervated by the subiculum, not just the accumbens. The implications of these additional dysfunctions for schizophrenic symptomatology are not considered, however. Such a narrow focus makes the model simple but unrealistic.

(7) Patients such as H. M. (Scoville & Milner 1957) with temporal lobectomy including the parahippocampal cortex have not been reported to experience schizophrenic symptoms, an ostensible difficulty for their model that Gray et al. do not address.

Neuro-developmental, brain imaging and psychophysiological perspectives on the neuropsychology of schizophrenia

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Attempts to construct a neuropsychological model of schizophrenia must contend with a wide array of relevant data. There are at least four sets of findings that Gray et al.'s model must take into account: (1) neuro-developmental findings, (2) findings on schizophrenics with predominantly negative symptoms, (3) brain imaging findings, (4) psychophysiological findings.

First, by focusing exclusively on a mechanistic interpretation of neuropsychological deficits in schizophrenia, the authors have failed to explain how the structural and neurochemical abnormalities underlying these deficits develop and change in the course of illness. In addition, since the model is based on descriptions of neuropsychological abnormalities in patients who are already schizophrenic, it is impossible to determine whether the model describes mechanisms at play only during acute episodes, or, more important, features of a long-standing vulnerability to psychosis. Of critical importance to this model is an explanation of changes in dopamine levels or receptor populations in the septohippocampal system; the authors suggest that these are centrally involved in the phenomenon of "overattention" in schizophrenia. To establish the hypothesis that abnormalities in these regions underlie overattention and other positive symptoms, it would be necessary to explain (1) evidence indicating that hippocampal abnormalities in schizophrenics are prenatal in origin (Falkai et al. 1988a; Jacob & Beckmann 1986; Kovelman & Scheibel 1984; McLardy 1974), (2) findings demonstrating that the offspring of schizophrenic parents show attentional disturbances and other deficits during infancy and childhood (Mednick & Silverton 1987), (3) why these symptoms become more severe at the onset of overt psychosis in early adult life, and (4) why attentional abnormalities and positive symptoms vary in the course of illness. The authors suggest that theirs is a descriptive model and therefore does not need to address issues of etiology. Failing to consider developmental questions renders the model of limited value, however. It is still necessary to explain *covariation* between the underlying structural and neurochemical pathology and *changes* in the expression of the behavioral phenomena to be explained (i.e., sensory filtering deficits, hallucinations, delusions).

A second limitation of the model is that it attempts to account for only the positive symptoms of schizophrenia. The authors attempt to justify this stance by suggesting that negative symptoms tend to follow the initial phase of positive symptoms and that negative symptoms reflect strategies to cope with defective filtering of sensory information. There are two difficulties with this approach. First, there is evidence that a subgroup of schizophrenics demonstrate predominantly negative symptoms early in their illness, as well as later, and that this subgroup shows relatively greater signs of structural brain pathology (Cannon et al. 1990). Second, very few schizophrenics can be characterized as having either purely positive or purely negative symptoms. Any model of schizophrenia that limits itself to an account of either positive or negative symptoms at best restricts the range of its explanatory power, and at worst fails to account for the phenomenon under scrutiny.

Third, the model ignores a substantial body of findings in the last decade from brain imaging studies of schizophrenics. Some of these findings are broadly supportive of the model, whereas others are not easily accounted for. Evidence of lateral ventricular enlargement in schizophrenia is consistent with volume reductions in such temporal-limbic structures as the hippocampal formation (Brown et al. 1986); similarly, third ventricle

enlargement is associated with reduced thickness of the diencephalic periventricular gray matter (Lesch & Bogerts 1984). Several studies have found an association between ventricular enlargement and cognitive dysfunction in schizophrenics as assessed by neuropsychological test batteries (Cannon, in press). This evidence supports Gray et al.'s hypothesis that limbic and thalamic regions play an important role in the expression of schizophrenic symptomatology. It is important to note, however, that schizophrenics with enlarged ventricles have been found to evidence predominantly *negative* symptoms (Shelton & Weinberger 1986). This evidence is not easily reconciled with a model linking limbic and thalamic pathology to positive symptoms. Other recent brain imaging findings not readily accounted for by the model include reduced parietal glucose metabolism (Cleghorn et al. 1989), structural abnormalities of the anterior corpus callosum (Raine et al., in press), and lateral asymmetries in temporal horn enlargement (Crow et al. 1989).

A related problem with the model is that it relies heavily on experimental lesion work in animals. Given the relative underdevelopment of cortex in animals relative to man, over-reliance on animal models will inevitably underemphasize the potentially critical role of cortical abnormalities in schizophrenic cognitive symptomatology. For example, prefrontal cortex makes up 29% of total cortex in humans, but only 12% in macaques and 3.5% in cats. Coupled with evidence for frontal dysfunction in schizophrenia from brain imaging studies (Weinberger et al. 1986), these data suggest that prefrontal cortical abnormalities are likely to have a major role in cognitive dysfunction in schizophrenics and should therefore receive a much greater emphasis in the model.

Another issue concerns the fact that language (which is largely lateralized to the left hemisphere) is critical for the expression of schizophrenia. A number of studies have found that structural abnormalities to the hippocampus and temporal cortex are lateralized to the left hemisphere (Altshuler et al. 1987; Crow, in press). Given the absence of language in animals, a neuropsychological model of schizophrenia heavily based on animal research will inevitably fail to account for these potentially important asymmetries.

A fourth limitation of the model is that it fails to incorporate psychophysiological findings relevant to attentional dysfunction in schizophrenia. In fact, these findings appear to support the concept of latent inhibition, which is a major focus of the model. For example, children of schizophrenics, after pre-exposure to a CS, have been found to give larger conditioned skin conductance responses when this CS is later paired with an aversive UCS (Mednick & Schulsinger 1968), thus indicating a lack of latent inhibition. Furthermore, individuals with these autonomic characteristics were found to be at increased risk for predominantly *positive* symptom schizophrenia in adulthood (Cannon et al., in press). These findings would have been predicted by the model if it had attempted to explain the development of the brain abnormalities underlying attentional dysfunction in schizophrenia within a neurodevelopmental framework. One psychophysiological finding not accounted for by the model, however, is that high-risk individuals with reduced skin conductance responses to novel stimuli have an increased risk for *negative* symptom schizophrenia. About 50% of schizophrenics are of this type. These schizophrenics evidence a different type of attentional disturbance, one based on undervigilance or underarousal. These findings again point to the need to address the full range of symptomatology in modelling the neuropsychology of schizophrenia.

What should a theory of schizophrenia be able to do?

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A theory of schizophrenia (or of other diseases manifesting themselves in behavior) needs to include body (chemistry, anatomy, neurology), behavior, and their interaction with each other and the environment, currently and as part of their history. As for theories in general, they must use the simplest processes as explanatory concepts.

To start with the latter, the two theories cited by Gray et al. use terms (weakening of stored memories and an inability to monitor "willed intentions") that are less fundamental than the basic concept of the immediacy theory (Salzinger 1984), which, I submit, is more suitable for their discussion.

The immediacy theory (in brief) states that schizophrenic patients tend to respond to those stimuli, external and response-produced, that are immediate in their environment. A number of consequences result from this simple premise, including that past memories, often but not always constituting remote stimuli, will appear to be weakened. It covers one of the theories proposed by the authors, therefore. Knowing that schizophrenic patients learn – that is, add to their reinforcement history – one can explain the smaller influence of past memories by appealing to the greater influence of the immediate stimuli. On the other hand, when an immediate stimulus evokes a response-produced memory, schizophrenics seem to have strong memories contrary to the theory espousing weakened memories as a basic fault in schizophrenia. Furthermore, immediacy theory applies to all areas of functioning, in perception, learning, language behavior, social interaction, and so forth.

As for the monitoring of so called "willed intentions" (a vague concept), this has no simple analog in neurological terms. Immediacy, on the other hand, suggests a correspondence between the way stimuli affect behavior and the way impulses move from one part of the nervous system to another. Furthermore, the dopaminergic hypothesis of schizophrenia suggests that responding to stimuli as they appear (immediate) would be more likely in schizophrenic patients than in normal people.

The behavioral data cited by the authors are consonant with the immediacy theory. Some are better interpreted by it than by the theories cited. As for other data cited for the immediacy theory, Salzinger (1984) showed, to give but three examples, that the behavior of schizophrenic patients can be conditioned at the same rate as that of normal individuals but is extinguished more rapidly in the former (Salzinger & Pisoni 1960). The absence of the reinforcing (immediate) stimuli during extinction was responded to more quickly by schizophrenics than by normal subjects. When schizophrenic patients and normals were instructed to keep an anchor weight from influencing their judgment of the heaviness of weights, the former were more influenced by the intrusion of that anchor than were normal individuals (Salzinger 1957). The proprioceptive stimulation of the weights was more immediate than the instruction. Finally, still another form of behavior, fluent speech, with its lowered communicability (comprehensibility) in schizophrenic patients, could be explained in terms of the shorter spans of influence of successive words over one another (Salzinger et al. 1970).

In contrast to Gray et al.'s interpretation of thought disorder as a *weakening* of moment-by-moment associations, the peculiar associations in schizophrenic speech are the result of their *greater control by immediate* rather than by remote words. Such an interpretation is buttressed by Chapman et al.'s (1964) finding that schizophrenic patients emit the strongest association to words irrespective of their context, thus seeming to emit idiosyncratic associations.

This leads us to another strength of the immediacy theory: It does not explain too much. It posits a single but basic difficulty, managing to explain as much as complicated theories try to do, by leaving room for other variables that interact with the basic deficit to round out the picture. Immediacy theory posits a tendency to respond to immediate stimuli, followed by behavior reinforced by immediate stimuli in the presence of stimuli that will act as further controlling stimuli later. Eventually the conditioning process will exaggerate the tendency to respond to immediate stimuli, unless deliberate therapeutic countervailing conditioning with more remote stimuli takes place. The theories used by Gray et al. burden themselves with having to explain all the symptomatology. Immediacy theory on the other hand, allows the subjects with the deficit to interact with their environment by the known laws of learning (and without assuming any deficit in these laws) to explain the considerable variety of schizophrenic symptomatology.

There is clearly insufficient space here to develop all the interactions, but two will exemplify them (for additional ones, see Salzinger 1984). Delusions of schizophrenic patients can be attributed to responding to stimuli out of context, a condition likely to occur when responding primarily to immediate stimuli. Thus a TV character scolding someone can be perceived by a schizophrenic as a personal message even though the context makes it clear that this is not so. As to thought disorder, findings on the speech of schizophrenic patients show that they respond to their own speech in very short segments, producing tangential thoughts because shorter spans of speech produce different (less restricted) associations from when they are embedded in controlling contexts of normal speakers.

In conclusion, Gray et al.'s neural explication is novel and useful because it relates behavioral data and theory to neural models. My only quarrel is with the authors' choice of behavioral theory and their failure to integrate their behavioral findings with reinforcement history in explicating the symptom picture of the patients. The schizophrenic patient's neural deficit is only the beginning of an explanation of schizophrenic behavior. To be successful, a theory must show how the neurological defect or difference relates to behavior and interacts with environments through learning and conditioning.

The significance of the basal ganglia for schizophrenia

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In their treatise on the neuropsychology of schizophrenia, Gray et al. propose a model that integrates the neural and cognitive aspects of the positive symptoms of schizophrenia. The key assumption is that positive symptoms arise from a disruption of input to the basal ganglia (in particular to the nucleus accumbens) from the limbic system (in particular, from the subiculum).

A major limitation of this hypothesis is that it deals with the pathogenesis of the positive symptoms of schizophrenia in isolation and, in fact, it presumes that separate mechanisms may underlie the positive and negative (defect) dimensions of the disease. Although Crow (1980a) suggested that positive and negative schizophrenia reflect two biologically and prognostically distinct schizophrenic subtypes, Andreasen's (1985) data indicated that the majority of patients have mixed syndromes. Subsequent studies by our group have found that these phenomena represent orthogonal components, coexist in the majority of patients, and are uncorrelated in the drug-free state (Kay et al. 1987; Kay & Singh 1989; Kay & Sevy, in press). A satisfactory model of schizophrenia, therefore, needs to account for both positive and negative manifestations as well as their co-occurrence in the same patient.

In discussing the anatomical regions implicated in schizophrenia, Gray et al. state: "Morphological studies of schizophrenic brain have failed to reveal any obvious abnormalities either in regions that are rich in dopaminergic cell bodies, or in regions rich in dopaminergic terminals." They draw attention to the neuronal connections between the hippocampal formation and the ventral striatum, concluding that they are crucial to the pathophysiology of positive schizophrenia.

The search for the neuropathology of schizophrenia dates back to Alzheimer (1897). Since then there has been no agreement on the specific pathological changes that underlie the symptoms of schizophrenia (cf. Stevens 1982). Three major pathologic studies (Lesch & Bogerts 1984; Nieto & Escobar 1972; Stevens 1982), however, have shown predilection to the periventricular regions of the diencephalon. This is in accord with neuroradiological studies that reveal a high prevalence of third ventricular enlargement in schizophrenia (Houston et al. 1986; Sandyk & Kay, in press b). Other investigators have reported pathological changes in the brainstem and implicate the reticular formation in the pathogenesis of the positive symptoms of schizophrenia (Fisman 1975).

In contrast to the statement of Gray et al., several investigators did find pathological changes in the basal ganglia of schizophrenic patients. Buscaino (1920) was the first to point out the involvement of the basal ganglia in the genesis of schizophrenic symptoms; he noted that serious alterations could be found, especially in the globus pallidus. Similar observations were reported in an extensive study by Hopf (1952). Woodard (1962) found Lewy bodies, identical to those seen in Parkinson's disease, in 25 of 224 (10.3%) of chronic schizophrenic patients over age 50, 26% of whom had Parkinsonism. Analysis of the distribution of the Lewy bodies revealed a predilection to the monoaminergic neurons of the substantia nigra and locus ceruleus; these findings are also characteristic of Lewy body distribution in patients with Parkinson's disease. More recently, Stevens (1982) described neuronal loss and gliosis in the basal ganglia in six of 28 schizophrenics, and Bogerts et al. (1985) subsequently found decreased volume of the internal pallidum in 13 schizophrenic patients in a morphometric study of the basal ganglia. These data indicate that pathological lesions in the basal ganglia are relevant to the schizophrenic disease process and may contribute not only to the motor symptoms of the disease, but also to the behavioral and cognitive deficits.

Biochemical and pharmacological studies have suggested that, in contrast to the positive symptoms of schizophrenia that are associated with increased dopaminergic and noradrenergic functions and decreased cholinergic activity (Frecska et al. 1985; Gay et al. 1989; MacKay 1980; Tandon & Greden 1989), negative phenomena are related to decreased dopaminergic and noradrenergic functions and increased cholinergic activity (Angrist et al. 1980; Bowers 1974; MacKay 1980; Stein & Wise 1971; Tandon & Greden 1989; Van Kammen et al. 1986). The profile of biochemical disturbances found in negative schizophrenia resembles, therefore, the one found in patients with Parkinson's disease (Sandyk & Kay, in press a; in press c). It is of interest that negative schizophrenia overlaps with Parkinsonism also with respect to the clinical symptoms (Sandyk & Kay, in press a). For example, motor retardation, poverty of speech, blunted affect, and cognitive impairment of the frontal lobe type are characteristic of both negative schizophrenia (Andreasen 1985) and Parkinsonism (Alpert & Rush 1983; Hoffman et al. 1987; van Putten & May, 1978). Hoffman et al. (1987) and Sandyk and Kay (in press a; in press c) described parallelism between these two disorders and suggested that they share common pathophysiological mechanisms. More recently, we found a significant association in schizophrenic patients between negative symptoms and positive glabellar tap reflex, which is pathognomonic for Parkinsonism (Sandyk & Kay, in press d).

By contrast with negative symptoms, the positive profile of schizophrenia has been related to increased dopaminergic activity (MacKay 1980). In Parkinsonism, such "positive symptoms" as hallucinations and delusions are seen in some patients who are treated with levodopa (Klawans 1988). These may accordingly be produced by excessive dopaminergic stimulation and may thus resemble pharmacologically the florid symptoms of schizophrenia. In addition, hallucinations and delusions are seen in nontreated Parkinsonian patients (Klawans 1988) and may reflect compensatory adaptive mechanisms in the striatum and mesolimbic dopamine system, which are aimed at increasing dopaminergic transmission (Sandyk & Kay, in press a; Zigmond et al. 1984). Similarly, we have proposed that the positive symptoms of schizophrenia reflect bursts of increased dopaminergic activity in the striatum and the mesolimbic dopaminergic systems (Sandyk & Kay, in press a; in press c). These compensatory mechanisms occur as long as dopaminergic projections are functionally intact. With the progression of the disease and with further degeneration of dopaminergic neurons in the basal ganglia and mesolimbic system, however, these compensatory mechanisms tend to attenuate, a phenomenon that may underlie the clinical observation that positive symptoms tend to decrease over time, whereas the negative symptoms may become more prominent (Pfohl & Winokur 1982).

In summary, we contend that the positive and negative features of schizophrenia bear strong resemblance to Parkinsonism, thus implying that disturbances of the *basal ganglionic* dopaminergic system may play a crucial role in the expression of schizophrenia. This hypothesis addresses the various clinical aspects of schizophrenia and considers the pathogenesis of the positive symptoms in the context of the negative syndrome. We conclude that the position of Gray et al., who view disruption of input to the basal ganglia as underlying the positive symptoms of schizophrenia, can only partially explain the nature of the positive symptoms.

NOTE

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Dopamine-GABA-cholinergic interactions and negative schizophrenic symptomatology

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The model proposed by Gray et al. illustrates the general difficulty inherent in attempts to correlate complex behavioral functions with defined neuronal networks, that is, to hypothesize about specific and testable functions of individual brain areas and connections while avoiding what might be termed hodological phrenology (see, for example, the functions attributed to the projections shown in Figure 4 of Gray et al.). Another probably typical feature of such models is the selection of some neuronal connections on the basis of functional considerations, whereas other, possibly more prominent anatomical connections, remain ignored without reason. Specifically, the fact that cholinergic neurons in the ventral pallidum appear to constitute the major target of the GABAergic output of the nucleus accumbens has been disregarded in the proposed model. This commentary focuses on the potential significance of changes in activity in GABA-cholinergic interactions in the basal forebrain as a result of dopaminergic hyperactivity within the nucleus accumbens.

The precise effects of the proposed weakening of the excitatory projections from the subiculum to the nucleus accumbens on the activity of the major output of the nucleus accumbens, that is, the GABAergic projection to the ventral pallidum/substantia innominata (Mogenson et al. 1983), are unclear. The experiments by Yang & Mogenson (1987a; 1989), Patel & Slater (1988), Swerdlow & Koob (1984), and others, however, suggest that inhibition of this GABAergic efferent projection may be a consequence of the loss of excitatory inputs and the resulting dopaminergic hyperactivity in the nucleus accumbens. As cholinergic neurons situated in the ventral globus pallidus (substantia innominata) are innervated by this GABAergic output (Ingham et al. 1988; Zaborszky et al. 1986), a reduced inhibition of the activity of cholinergic corticopetal neurons will follow (Yang & Mogenson 1989; for a review of the evidence for basal forebrain GABA-cholinergic interactions, see Sarter et al. 1990). Consequently, cortical cholinergic hyperactivity may be the end result of dopaminergic hyperactivity in the nucleus accumbens as proposed by Gray et al.

Several lines of evidence have suggested that cholinergic hyperactivity may be implicated in the pathogenesis of negative schizophrenic symptoms (for review see Tandon & Greden 1989). Furthermore, the administration of L-dopa and amphetamine, compounds known to exacerbate schizophrenic symptoms, increases cortical acetylcholine release via D2 receptors (Beani & Bianchi 1973; Casamenti et al. 1987). Thus, both anatomical and neuropharmacological evidence supports the hypothesis that cholinergic hyperactivity may result from dopaminergic hyperactivity and that the basal forebrain dopamine-GABA-cholinergic link represents the anatomical substrate of such an interaction. Therefore, by implicating the effects of dopaminergic hyperactivity on the main target neurons of the GABAergic output of the nucleus accumbens into the proposed circuitry, the model of Gray and his colleagues may be extended to the pathophysiology of negative symptoms.

Such an extended model would predict that muscarinic antagonists, GABA-mimetic drugs, and even neuroleptics should exert some beneficial effects against the negative symptoms in schizophrenia. As summarized by Tandon & Greden (1989), several studies have demonstrated that anticholinergic drugs are indeed effective against negative schizophrenic symptoms. Furthermore, although neuroleptics are typically ineffective for negative symptoms, neuroleptics that show a very high anticholinergic potency (clozapine and zotepine) were found to be beneficial in this regard (Fleischhacker et al. 1987). Data on the effects of GABA-mimetics on negative symptoms in schizophrenia appear unavailable.

Although on the basis of anatomical and neuropharmacological findings it is compelling to speculate about the effects of dopaminergic hyperactivity in the nucleus accumbens on cortical cholinergic activity, the idea that cholinergic *hyperactivity* in schizophrenia is involved in the negative syndrome appears difficult to accept if we also consider the role of acetylcholine in other neuropsychiatric diseases. Specifically, in senile dementia, the cardinal symptoms have been related to a cholinergic *hypoactivity* (e.g., Cummings & Benson 1987). As some of the negative schizophrenic symptoms (Andreasen 1982) are akin to some of the symptoms that occur at later stages in senile dementia (Reisberg 1983), it would seem logical to conclude that both cholinergic hyperactivity and hypoactivity may be involved in comparable behavioral conditions. This paradoxical situation could be resolved by a closer inspection of the properties of acetylcholine in the cortex and of the effects of pharmacological stimulation and blockade of the cholinergic system. The proper function of the cholinergic system appears to depend on a defined pattern of transmission. Both stimulation and blockade of the cholinergic system disrupt this patterning and dissociate postsynaptic events from presynaptic activity (Sarter et al. 1990). Thus, both cholinergic hyper- and hypoactivity may indeed account for comparable impairments of behavioral functions.

The idea that dopaminergic hyperactivity in the nucleus

accumbens causes a cortical cholinergic hyperactivity that is associated with negative symptoms would suggest that positive and negative symptoms are necessarily correlated. Such an interaction, on the one hand, conflicts with arguments supporting a dichotomization of positive and negative subtypes (Crow 1985), but, on the other hand, it fits with the fact that most schizophrenic patients exhibit a mixture of positive and negative symptoms (Rosen et al. 1984).

The model proposed by Gray et al., as well as its extension into the basal forebrain GABA-cholinergic interactions discussed herein, appears to be speculative but is nevertheless heuristically powerful. The model awaits clarification with respect to (1) the assumption that the temporal lobe pathology in schizophrenia (Roberts 1990) indeed results in dopaminergic hyperactivity in the nucleus accumbens, (2) the clarification of the interactions between dopamine, excitatory amino acids, and the cholinergic interneurons in the nucleus accumbens (Russell et al. 1989), (3) the effects of dopaminergic hyperactivity in the nucleus accumbens on the activity of its GABAergic efferent projection, (4) the hypothesis that dopaminergic hyperactivity in the nucleus accumbens results in an increase in cortical cholinergic transmission as proposed in this commentary, and (5) the assumption that cholinergic hyperactivity is involved in the negative symptomatology (Tandon & Greden 1989). One hopes that these and further questions arising from the model proposed by Gray and colleagues will re-activate the interest in basic research on the neurobiology of schizophrenia.

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A hippocampal theory of schizophrenia

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Gray et al. present a neuropsychological model suggesting that a disruption of an input to the basal ganglia from the subiculum explains positive symptoms in schizophrenia; this integrates with Gray's (1982) model of septohippocampal function. Gray's (1982) model proposes that the septohippocampal system compares predicted with actual states of the world; if there is a mismatch the system brings the current behavior to a halt and directs exploratory behavior toward the novel event. Gray et al. propose that the mismatch signal is transmitted to the nucleus accumbens through the subiculum. Whereas we agree with Gray et al.'s postulate regarding a hippocampal impairment in schizophrenia, we dissent from the hippocampal model that they present and its mapping on the limbic-mesencephalic circuits.

Gray et al. presents ideas similar to these advanced by Schmajuk (1987) and Schmajuk & Tyberg (1990). Schmajuk (1987) had shown that hippocampally lesioned animals are adequate animal models of schizophrenia because (1) schizophrenia might be the consequence of hippocampal damage, (2) animals with hippocampal lesions share many of the characteristics of schizophrenics in both cognitive and psychophysiological processes, (3) hippocampal dysfunction seems to be present in schizophrenia, and (4) the effects of hippocampal lesions might be reversed by neuroleptics. In the same line, Schmajuk and Tyberg (1990) suggested that (1) schizophrenia is the result of disorientation of hippocampal pyramidal cells, loss of entorhinal cortical cells, or disarrangement in cingulate cortical cells; (2) these pathological alterations translate into a functionally altered hippocampal function as described by an attentional model of hippocampal function (Schmajuk & Moore 1988); (3) this attentional impairment underlies the changes in cognitive and psychophysiological processes found in schizophrenic patients and hippocampally lesioned animals; (4) abnormal behavior is improved by neuroleptics because they compensate for the lack of the normal hippocampal modulatory effects on the nucleus accumbens.

Because Gray et al. introduce a view of schizophrenia congenial with ideas fostered in our previous papers, this commentary concentrates on the similarities and differences between their notions and our own. Because space is limited, we concentrate on a classical conditioning paradigm (blocking) found to be impaired in both hippocampally lesioned animals and schizophrenic patients.

Schmajuk and Tyberg (1990) offered a model of hippocampal-accumbens interactions that describes attentional processes in normal and pathological behavior. As shown in Figure 1, the nucleus accumbens receives a glutaminergic excitatory input from the hippocampus via the subiculum and a dopaminergic inhibitory input from the ventral tegmental area. Activation of dopaminergic neurons that originate from the ventral tegmental area attenuates the excitatory response of the nucleus accumbens to hippocampal stimulation (Yang & Mogenson 1987b). The GABAergic output of the nucleus accumbens inhibits ventral pallidal and subpallidal areas. In turn, ventral and subpallidal areas activate *and* inhibit the mesencephalic locomotor region (Yang & Mogenson 1987b), which controls exploratory and orienting movements. When the hippocampal output increases, it activates the nucleus accumbens, which *inhibits* subpallidal areas, which in turn disinhibit the mesencephalic locomotor regions, thereby increasing locomotion. This activation is counteracted by dopaminergic stimulation of the nucleus accumbens. Dopamine inhibits the nucleus accumbens, which *disinhibits* subpallidal areas, which in turn excite the mesencephalic locomotor regions, thereby increasing locomotion. Dopaminergic inhibition of the nucleus accumbens is counteracted by the hippocampal output. Therefore, *imbalance* between hippocampal and dopaminergic inputs to the nucleus

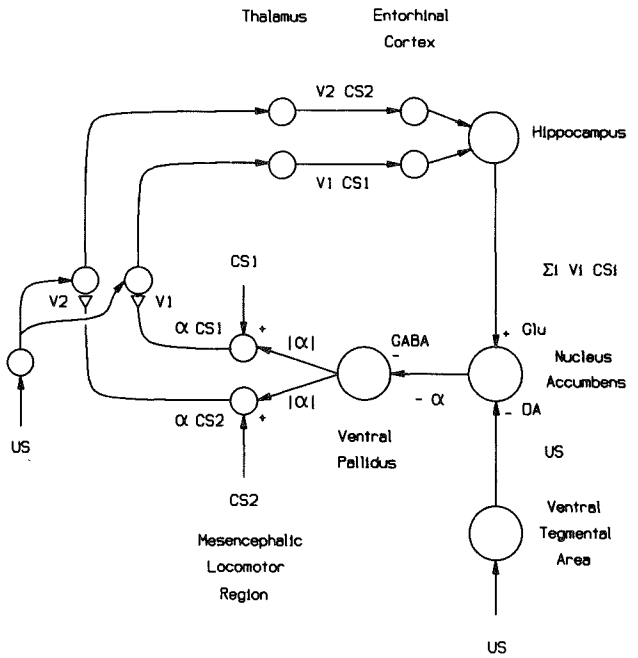

Figure 1 (Schmajuk & DiCarlo). An attentional model of hippocampal function. CS_1 and CS_2: conditioned stimuli, US; unconditioned stimulus, V_1 and V_2: CS-US associations. Arrows represent nonmodifiable synapses. Triangles represent plastic synapses. After Schmajuk & Tyberg (1990).

accumbens *increase* exploratory and orienting movements in the mesencephalic locomotor regions.

Schmajuk (1989; Schmajuk & Moore 1985; 1988) introduced a real-time attentional model of classical conditioning, designated the S-P-H model. Briefly, when a conditioned stimulus (CS) is followed by an unconditioned stimulus (US), an association, V, is formed; this association can be regarded as the prediction of the US by the CS. In the model, associations between CSs and the US are controlled by the attentional term α (Pearce & Hall 1980), which is proportional to the *mismatch between the actual and the aggregate prediction of the intensity of environmental events*, such as the US. α is also proportional to the intensity of the orienting response. According to the "aggregate prediction" hypothesis (Schmajuk 1984), the *hippocampus computes the aggregate predictions of environmental events*. The aggregate prediction is used to compute α, which modulates associative learning. The model describes the transition from voluntary ($\alpha > 0$) to automatic behaviors ($\alpha = 0$) during associative learning (see Pearce & Hall 1980). The "aggregate prediction" hypothesis of hippocampal function provides accurate descriptions of the effect of hippocampal lesions in numerous classical conditioning and spatial learning paradigms (Schmajuk 1989; 1990). In addition, the model describes the increase in the activity of hippocampal pyramidal cells during classical conditioning trials, as described by Berger and Thompson (1978).

Figure 1 shows how variables in the S-P-H model can be mapped onto different brain regions (Schmajuk & Tyberg 1990). The association of CS_1 with the US, V_1, and the association of CS_2 with the US, V_2, may be stored in different brain areas depending on the type of task (e.g., cerebellum in the case of classical conditioning). Neurons in entorhinal cortex receive information about the associations established by CS_1 and CS_2 with the US (Berger & Thompson 1978). Hippocampal output to the nucleus accumbens is proportional to the aggregate prediction of the US, $V_1\ CS_1 + V_2\ CS_2$. We assume that the dopaminergic input is proportional to the activating value of the US (Beninger 1983; Colle & Wise 1988). Because the imbalance between hippocampal and dopaminergic inputs to the nucleus accumbens *increases* orienting movements in the mesencephalic locomotor regions, orienting responses increase when there is a mismatch between the US and the aggregate prediction of the US. Activity in the mesencephalic locomotor region is therefore proportional to $\alpha = |US - (V_1\ CS_1 + V_2\ CS_2)|$, that is, the absolute value of the difference between the US and its aggregate prediction. At the beginning of learning, the aggregate prediction, $CS_1\ V_1 + CS_2\ V_2$, is very small and the hippocampus sends a weak excitatory signal to the nucleus accumbens, which is in turn activated by the US, thereby activating the generation of orienting responses in the mesencephalic locomotor system (α is large). With learning, the prediction of the US increases, and the hippocampus increases the excitation of the nucleus accumbens, which in turn decreases its activation of orienting responses (α becomes small). In the case of blocking, when CS_1 predicts the US, orienting responses are inhibited and the animal does not acquire an association between CS_2 and the US. Because after hippocampal lesions aggregate predictions are no longer computed, α equals the value of the US and does not decrease as learning proceeds. The S-P-H model therefore predicts that animals with hippocampal lesions and schizophrenic patients do not show blocking.

According to Figure 1, hippocampal lesions and elevated dopamine activity have similar effects: They disrupt the balance between hippocampal and dopaminergic inputs to the nucleus accumbens, thereby increasing orienting responses and impairing selective attention to relevant stimuli. A possible site for haloperidol action is the nucleus accumbens. If schizophrenia is related to a decreased, defective hippocampal input to the nucleus accumbens, blockade of the dopaminergic input reinstates the equilibrium and decreases the abnormal generation of orienting responses, thereby normalizing attention.

Table 1 compares the performance of schizophrenic patients with (a) the effect of hippocampal lesions in different tasks and (b) with descriptions generated with the S-P-H attentional model under the aggregate prediction hypothesis. In most cases (a) the hippocampally lesioned animal model and (b) the S-P-H computational model are able to reproduce the characteristics of schizophrenics in both cognitive and psychophysiological processes.

Table 1 (Schmajuk & DiCarlo). *Comparison between schizophrenic symptoms, the effect of hippocampal lesions, and the predictions generated by the S-P-H attentional model of the hippocampus in different experimental paradigms.*

	Schizophrenia	Hippocampal lesion	S-P-H model
1. Selective attention	Deficit	Deficit	Deficit
2. Acquisition of classical conditioning	Facilitation	Facilitation	Facilitation
3. Extinction of classical conditioning	Deficit	Deficit	Deficit
4. Generalization	Increased	Increased	Increased
5. Spatial effects	Deficit	Deficit	Deficit
6. Contextual effects	Deficit	Deficit	Deficit
7. Serial position curves	Deficit	Deficit	Deficit
8. Recognition memory	Normal	Deficit*	Deficit
9. Complex learning	Deficit	Deficit	Deficit
10. Stereotyped behavior	Increased	Increased	?
11. Superstitious behavior	Increased	Increased	?
12. Discrimination reversal	Deficit	Deficit	Deficit
13. Arousal	Increased	Increased	Increased
14. Habituation of the orienting response	Deficit	Deficit	Deficit
15. Skin conductance recovery	Facilitated	Facilitated	?
16. Event-related potentials	Attenuated	Present	?
17. Heart rate	Normal	Normal	?
18. Polydipsia	Present	Present	?

Note. Symbols:* The animal model fails to describe the schizophrenic symptom accurately. ? The theoretical model cannot describe the experimental result. From Schmajuk & Tyberg (1990).

Although the S-P-H and Gray et al.'s models can be easily compared with mathematical formalisms, such treatment is beyond the scope of the present commentary. We therefore compare both models in the following terms. In contrast with Schmajuk & Tyberg's (1990) assumption that the hippocampal output to the nucleus accumbens is proportional to the aggregate prediction of environmental events, Gray et al. consider that the hippocampal output is proportional to the mismatch between actual and predicted events (α, in our terminology). Whereas in the S-P-H model learning is controlled by mismatch signals (acquisition stops when $\alpha = 0$), in Gray et al.'s model acquisition is enhanced (but not controlled) by mismatch signals (acquisition may proceed even when $\alpha = 0$). According to the Gray et al. model, during the first phase of blocking (CS_1 is presented with the US) the mismatch is large (because the US is underpredicted), and the hippocampus activates the generation of orienting responses, bolstering acquisition. Because learning is not controlled by hippocampal operation, however, it may not stop even with zero mismatch (when the hippocampal output is zero). As learning proceeds, the mismatch may increase again (because the US is now overpredicted), and learning is further boosted. Therefore, according to Gray et al.'s model, mismatch signals at first decrease but, as training progresses, they may increase again. Consequently, during the second phase of blocking (CS_1 and CS_2 are presented with the US), CS_2 may receive a stronger hippocampal thrust than CS_1 obtained during phase one. Under these circumstances, Gray et al.'s model may not be able to describe blocking. In addition to its potential problems in blocking, because normal (but not hippocampal) learning is assisted by mismatch signals, Gray et al.'s model wrongly predicts that normal animals learn faster than hippocampally lesioned animals. The S-P-H model correctly portrays acquisition and blocking in both normal and hippocampally lesioned animals (and schizophrenics).

In summary, in agreement with Schmajuk (1987) and Schmajuk and Tyberg (1990), Gray et al. add arguments in favor of a hippocampal view of the positive symptoms of schizophrenia. Less convincing is their description of limbic-mesencephalic interactions in terms of Gray's (1982) model of hippocampal function. The assumption that mismatch (α) is computed in the hippocampus may not be able to generate accurate descriptions of normal behavior and of the effects of hippocampal lesions (and schizophrenic disorders) on several learning paradigms. Regardless of these difficulties, Gray et al.'s attempt to describe a psychopathological disorder in terms of brain dysfunction remains extremely valuable.

A plausible theory marred by certain inconsistencies

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The theory propounded in the target article reflects a thoroughgoing familiarity with cognitive dysfunction in schizophrenia and neural mechanisms controlling attention and "motor programs." My lack of expertise in this area does not permit me to judge the plausibility of the authors' neuropathological speculations, but I can, with some confidence, endorse the plausibility of what the authors conjecture to be the central or primary roots of cognitive dysfunction in positive schizophrenia. More generally, I have the impression that this neuropsychological theory of schizophrenia has heuristic value, and I agree with the authors that the theory has the virtue of being eminently testable.

Any major effort to build a theory regarding the complex phenomena that characterize schizophrenia will show inconsistencies and pieces of evidence that do not fit well into the overall framework of the theory. It is to these issues that my comments will be addressed.

Gray et al. advance the view that the positive symptoms in the acute phase of the illness are eventually replaced by negative symptoms as chronicity sets in and, indeed, that negative symptoms may be a defense against the terror and confusion associated with delusions and hallucinations. There is evidence (e.g., Andreasen 1985), however, that there are "mixed" cases in which both positive and negative symptoms in the same individual endure over extended periods of time. A case can probably be made that the number of schizophrenics in whom only positive symptoms occur during an acute episode is relatively small.

Mixed cases pose a problem for the present theory, which accounts only for positive symptoms in patients in whom these symptoms are dominant during the acute phase. The question needs to be raised: Does the theory apply with equal force to delusions and hallucinations in acute patients in whom both positive and negative symptoms coexist?

In a related connection, a form of cognitive dysfunction that has a robust history of replication – segmental set (the inability to maintain a major set to an impending event, Shakow 1962) – fits well with Hemsley's hypothesis of the weakening of the influence of stored memories of regularities of previous input on current perception, but not with the dopaminergic activity hypothesis, because it has been shown to be resistant to normalization by dopamine blocking neuroleptics (Spohn & Coyne 1989). Similarly, smooth pursuit eye movement impairment (Levin 1983; 1984), which is seen to be consistent with dopaminergic neural dysregulation hypothesis, is also not normalized or affected in any way by neuroleptics (Spohn et al. 1988).

I have some difficulty accepting Hemsley's hypothesis as an all-pervasive account of primary dysfunction. After all, positive symptom schizophrenics in an acute episode learn to negotiate the physical environment of hospitals, learn the names of hospital personnel, do not forget the names of visiting family members, and keep appointments. This clearly implies that any weakening of the influence of stored memories of regularities of previous input on current perception is a circumscribed and, to an unknown extent, limited deficit in positive symptom schizophrenics.

This brings me to what I consider to be the most serious weakness of Gray et al.'s theory. The authors place a high degree of reliance in theory development on animal studies of latent inhibition, the blocking effect and the partial reinforcement extinction effect. They present evidence that in untreated animals stimuli exposed prior to a learning task in which the preexposed stimulus has signal significance slows learning or reduces extinction because preexposed stimuli then signalled nothing of significance. These phenomena are "abolished" by a dopamine releasing psychotomimetic drug, however, The authors explain the latter findings on the basis of a Hemsley hypothesis-derived deficit, namely, "overattending" to irrelevant or nonsignal stimuli.

There are two problems with this construct, which is so critical to the theory. Braff et al. (1978) have shown that schizophrenics *disattend* a pulse preceding a startle stimulus and, thus, their startle response is not diminished as it is in "prepulsed" normals. Bernstein et al. (1982) have reported that between 40 and 50 percent of all schizophrenics do not manifest an orienting response to innocuous, neutral stimuli. Even Patterson et al. (1987), whose "failure of contextually generated expectancy" hypothesis is cited as congruent with Hemsley's hypothesis, add to the evidence adduced here that many schizophrenics under certain circumstances disattend both irrelevant and relevant stimuli. These authors report a diminished event related potential (ERP) registration response in schizophrenics when ERP is recorded during the performance of a backward masking task.

The implication of the foregoing is that under some circum-

stances positive symptom schizophrenics may disattend relevant and irrelevant stimuli, and under others they may "overattend." The task for the theory here is to specify conditions under which either of these phenomena may occur.

The second problem with Gray et al.'s interpretation of the above-cited animal studies is that Hemsley's hypothesis would seem to predict slower rather than faster learning in dopaminergic animal subjects. For example, in the conditioning phase of the blocking effect paradigm, one could consider the repeated association of UCS with CS1 and CS2 as inducing "stored memories of regularities of previous input" and a weakening of the influence of these stored memories on current perception of repeated trials as leading to slowed learning.

Gray et al. may well reply: Yes, but both animal studies and studies of latent inhibition in acute and chronic schizophrenics confirm that faster learning involving preexposed stimuli took place in subjects in a presumably dopaminergic state: "Overattending" in the reported studies does not, however, necessarily account for faster learning in these studies. There are no indications that preexposure of stimuli was controlled for in studies in which rate of learning without preexposure was examined in both dopaminergic and nondopaminergic subjects. Thus, it may well be that dopaminergic conditions, independently of overattending, may, under some conditions, lead to faster learning.

I want to raise two last questions (of lesser import than the foregoing). Why was there no effort to integrate with the theory substantial evidence of cerebral lateralization of dysfunction in schizophrenia? And, is the theory compatible with the fact that the onset of schizophrenic disorder does not occur until late adolescence or early adulthood?

What is schizophrenia?

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Gray et al. have constructed a neuroanatomical model designed to explain some of the symptoms and characteristics of schizophrenia. We have reservations about their conceptualization of both the pathological neural substrate and their approach to the cognitive symptoms of schizophrenia, which we discuss in turn.

In the search for an anatomical basis of the illness, two clues are accepted:

(1) The dopamine hypothesis based on the amelioration of schizophrenic symptoms by DA blocking neuroleptics and exacerbation of symptoms by dopaminergic agents.

(2) Reported shrinkage (atrophy?, dystrophy?) of the hippocampus.

As the nucleus accumbens is the dopamine biased target of the hippocampus, it is postulated that this area should be a major site of the pathophysiology of the illness. In fact, the "productive" or "positive" symptoms of schizophrenia (hallucinations, delusions, feelings of dread and strangeness), draw one to the temporal lobe. Guided by the dopamine hypothesis, one scarcely requires the Hemsley & Frith psychological hypotheses to come up with an anatomic meeting point in the nucleus accumbens. One explanation could be that degeneration or failure of maturation of certain hippocampal projections to accumbens could cause enhanced dopamine activity in nucleus accumbens through heterotypic sprouting of DA fibers that project to the dendrites of the same spiny neurons (Totterdell & Smith 1989). There is precedent for this explanation in the experimental literature. In now classical studies, Raisman (1969) showed that after transection of the fimbria-fornix – the major pathway that connects the hippocampus with the septum (and nucleus accumbens) – degenerating terminals and vacated synapses in the septal nuclei are replaced by new synaptic contacts derived from the medial forebrain bundle. Moore et al. (1971) subsequently showed that the sprouting fibers that replace degenerating fornix terminals belong to the ascending noradrenergic pathway. The functional significance of the growth of catecholamine fibers into synaptic sites previously occupied by glutamatergic axons is still unknown. As suggested by recent studies of epilepsy, survival and function of regenerated axons may have important consequences (Tauck & Nadler 1985; Sutula et al. 1988).

If sprouting of DA or NE fibers occurs in schizophrenia, we would expect increase in these neurotransmitters in the nucleus accumbens or septum. Indeed, this has been reported by several authors, although not consistently supported by other studies, a result that may be from pooling data from inexactly matched tissue samples or disparate cases. Supporting the sprouting hypothesis are the experimental data cited by Gray et al. demonstrating increased DA turnover in nucleus accumbens 28 but not seven days after hippocampal lesion.

A second possibility, favored by Gray et al., is that D2 binding sites expand in response to decreased hippocampal (subicular) input. This would be a somewhat unexpected result – one might rather expect glutamate receptor expansion from loss of glutamatergic subicular projections. Although earlier studies favored up-regulation of D2 binding sites, more recent studies with both autoradiography and PET show no increase in D2 binding sites in untreated schizophrenics and therefore implicate the neuroleptic drugs as the major source of the up-regulation reported in earlier studies (Farde et al. 1990; Kornhuber et al. 1989). The importance of up-regulation in a few cases may be lost in the pooling of data from many cases. Outliers may be important to study more closely.

A third possibility, not cited by Gray et al., is that a decrease in tonic inhibition of A10 neurones by GABA feedback could directly increase DA overactivity in nucleus accumbens. This model was explored in experiments in which microamounts of the GABA blocking agent, bicuculline, were injected into A-10 area of waking cats with chronic intracerebral cannulas and electrodes (Stevens et al. 1974). Following instillation of a few micrograms of bicuculline in the ventral tegmental area, behavioral and EEG changes ("hallucinatory" activity and "septal spikes") were consistent with behaviors and depth EEG changes (Heath 1954) reported in schizophrenia. Kindling of the A10 area produced similar but less dramatic changes (Stevens & Livermore 1978). Attempts to demonstrate reliable changes in DA metabolism in nucleus accumbens after bicuculline instillation in VTA of rats failed to provide consistent changes in tyrosine hydroxylase there. Although individual animals demonstrated a marked increase in this measure of DA turnover, significant results were not obtained after pooling data, doubtless a result of variability of injection site in a very complex region of closely adjacent pathways (unpublished observations, 1976).

Based on their anatomic hypothesis, Gray et al. propose that "positive" schizophrenic symptoms (thought disorder, hallucinations, overattention) arise from a "disruption" in the normal function of the input to nucleus accumbens. What is the function of that input? This is not spelled out clearly. Nor is the relation of the septohippocampal cholinergic projection as discussed here integrated in their model. The series of complex experiments on the rat appears to support a disturbance in motor sequencing that could, by a stretch of the imagination, have some parallels in thought sequencing.

Although the authors may be on target anatomically in focusing on projections of a dystrophic hippocampus or parahippocampal gyrus, we need mechanisms beyond their proposed loss of motor sequencing to account for the diverse symptoms of this illness.

The proposed model of psychological mechanisms in the formation of schizophrenic symptoms is limited. It accounts most easily for symptoms such as "made acts" through the

mechanism of faulty intention monitoring. This is a relatively rare symptom, however. The model does not address so called "negative" or defect symptoms that are common and probably fundamental to the illness. Also lacking is any discussion of the intellectual deficits that have been amply documented in schizophrenia (Levin et al. 1989). Although it is the author's prerogative to decide which symptoms need to be modelled, the fact that neither "negative" symptoms such as blunted affect nor intellectual impairment are addressed directly is a critical limitation.

Several features of the model of positive, productive symptoms appear to be strained. The idea that hallucinations are subvocal speech or thoughts with a missing link to the intention monitor, misattributed to the external environment, has a certain appeal. The misattribution model, however, does not explain why anyone would speak to himself in such a fashion. That is, the proposed mechanism does not begin to explain the origins of the unusual content that is so frequently encountered in hallucinatory phenomena. To suggest that these statements may stem from long term memory is also strained: Many hallucinations are new creations that have never been heard previously. The proposed mechanism, therefore, seems unable to account for important features of the very symptoms singled out for discussion.

The discussion of "overattention" also seems to strain the limits of the concepts of automatic attentional processes. It seems more accurate to say that patients with schizophrenia generally derive less meaning and coherence from a variety of visual, auditory, and linguistic stimulus presentations than do normal controls (Koh 1978; Schwartz et al. 1980). This may result in their being aware of only certain features of a particular presentation. They are not features that normal subjects are unaware of as a rule, but features that are secondary to the usual focus of attention on Gestalt characteristics, organized elements, and the semantic relatedness. Whereas this distinction may be minor, there is an important difference between the intrusion into awareness of cognitive elements that are usually processed outside of consciousness and a failure of cognitive operations resulting in unorganized focal attention. In short, there is no doubt that schizophrenia involves attentional abnormalities. The problem, however, at least in cases of established illness, more often appears to be one of too little attention rather than "overattention" (Nuechterlein & Dawson 1984).

In light of the centrality of attentional impairment in the genesis of symptoms in the proposed model, several important research findings are difficult to explain. Attentional deficits persist throughout the course of the illness, often with little relation to the types of clinical symptoms discussed by the authors; these may be present in children at genetic risk for the illness who have no psychotic symptoms (Nuechterlein & Dawson 1984). These types of attentional impairments are often not highly intercorrelated, exhibiting a modest relationship to other measures of neuropsychological performance (Kopstein & Neale 1972). Although neuroleptic medications may improve attentional performance and clearly provide dramatic relief for many patients from the hallucinations and delusions discussed by Gray et al., the impact of these medications on other cognitive measures is quite modest (Gold & Hurt 1990; Medalia et al. 1988). There appears to be a partial dissociation of symptomatic, attentional, and neuropsychological measures in schizophrenia, therefore. These data are a challenge for any model that attempts to explain the formation of symptoms in terms of attentional mechanisms. If attentional mechanisms are involved in the genesis of hallucinations and delusions, therefore, they are different from the forms of attention that are required by most neuropsychological tasks. Once this distinction is made, the appeal of linking attentional abnormalities to symptom generation is diminished considerably.

Neuropsychology of schizophrenia: The "hole" thing is wrong

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In the classical work, "A Proposed Mechanism of Emotion," James Papez (1937) took the initial bold steps toward defining the functional interactions in limbic circuitry. Subsequent developments in anatomical, electrophysiological, neurochemical, and behavioral investigations have refined our understanding of the organization and infrastructure of cortico-striato-pallido-thalamic (CSPT) circuitry to a point where useful circuit models can be constructed for several neuro- and psychopathologies (Penney & Young 1983; Swerdlow & Koob 1987a). These models have utility as heuristic tools, but, more important, they promote the concept that complex behavioral pathology must reflect a disturbance in dynamic interactions between interconnected circuitry rather than a single localized "lesion" in an isolated brain structure. In other words, they emphasize the contribution of the "whole" limbic circuit – rather than the "hole" in limbic circuitry – to behavioral pathology. In their target article, Gray et al. offer several new and important modifications to previous models of cortico-striato-pallido-thalamic circuitry (Carlsson 1988; Penney & Young 1983; Swerdlow & Koob 1987a).

Most important, Gray et al. relate Frith's (1987) and Gray's (1982a; 1982b) "circuit" diagrams with respect to several neuropsychological constructs – for example, attention, intention, behavioral inhibition, LTM, habituation, and other conditioning phenomena – to parallel and overlapping models of CSPT interactions. This work expands on Gray's earlier description of "approach/inhibition" circuitry contained within subiculo-accumbens and septohippocampal connections (Gray & Baruch 1987). In so doing, the authors begin to fill the "psychological void" created by previous neurologically oriented models of limbic organization (see Gray & Baruch 1987; Penney & Young 1983; Swerdlow & Koob 1987a). Second, they describe putative circuit interactions in much greater detail than exists in earlier models. The "skeleton" of this circuitry – three interacting "loops" of neuronal connections based on a model by Penney and Young (1983) and modified slightly later (Swerdlow & Koob 1987a) – has been tested and supported (at least partly) by studies of metabolic activity in CSPT structures in normal and schizophrenic subjects (Wu et al. 1990). The details added by Gray et al. are most evident in expanded descriptions of septohippocampal, amygdalo-accumbens, and subiculo-accumbens circuitry, the prefrontal cortex (although still largely a "tacked on" enigma for this circuit wiring), the interaction of dorsal ("motor") and ventral ("limbic") components of this circuit, and the description of "output" effectors in the superior colliculus and pedunculopontine nucleus (although the role of the latter structure as a limbic "output" remains controversial, see Swerdlow & Koob 1987b). Finally, the authors expand on their previous description of several animal models of psychopathology – particularly latent inhibition (LI) and the partial reinforcement extinction effect (PREE) – and relate them to both their proposed neuropsychological and neuroanatomical circuitry. Most important, the emphasis – even with these animal models – must be that cognitive and behavioral deficits are based on "whole" circuit dysfunction, rather than on a single localized lesion.

In addition to outlining overlapping psychological and neuroanatomical circuit disturbances in schizophrenia, Gray et al. set forth many lofty goals for their model in their second paragraph. While they have gone a long way toward reaching these goals, it is one purpose of this commentary to focus on where they have not gone "far enough." Specifically, several important issues are not resolved by this model.

First, while psychological models by Frith (1987) and Gray (1982a; 1982b) focus on cognitive or emotional processes, the core of the model circuitry presented by Gray et al. in their target article relates to motor function. Thus, as reviewed by the authors in their main assumptions (sect. 9) and the subsequent discussion, the primary function of their proposed circuitry relates to the initiation and "switching" of "motor programs." Nonetheless, schizophrenia – unlike Parkinson's disease, Huntington's disease, tardive dyskinesia, Tourette's syndrome, and other neurological disorders of the basal ganglia – is not primarily characterized by disturbances of motor initiation or switching. Certainly, to paraphrase the authors, it is the cognitive and emotional disturbances by which schizophrenia is defined (Gray & Baruch 1987).

Clearly, Gray et al. mean to apply this same brain circuitry, as well as the principles of motor initiation, timing, and switching, to the structure and organization of perception, thought, and emotion in schizophrenia. Neural circuitry must account not only for disturbances in information processing and associations that characterize the acute cognitive dysfunction in schizophrenia, but it must also account for the more pervasive thought patterns of schizophrenia – including delusions of persecution, ideas of reference, thought broadcasting and insertion, depersonalization, magical thinking, and indeed disturbances of ego and identity. This is not to say that the current model must explain schizophrenia at this level of complexity, for we do not yet understand enough about the brain to accomplish this feat. It is certainly easier to conceptualize and design experiments to test limbic-basal ganglia interactions as they relate to motor phenomena. For example, it is easier to model the neuronal impact of novel cues on fixed purposeless motor sequences (stereotypy) than it is to model the neuronal impact of novel cues on fixed irrational belief systems (delusions). With the sophistication of the psychological models presented by Gray et al., however, it should be possible to ascribe to this neural circuitry more complex functions that might serve as substrates for the true "core" schizophrenic symptomatology.

Models never go far enough, and another shortcoming of this model is that Gray et al. do not identify specific circuit modifications to account for the numerous different clinical presentations of schizophrenia. The authors open with the disclaimer that they have "chosen to concentrate" on acute, positive aspects of schizophrenia, but although this is an advantage in the sense of being easier, it may lead us to misjudge critical properties of CSPT circuitry that might in turn provide clues to circuit relationships. One major conceptual advantage of the "circuit dynamic" versus "lesion" approach to psychopathology is that the heterogeneity of clinical presentations can actually be an advantage in helping us piece together the circuit: Whereas a "primary" disturbance at any level of this circuit (e.g., limbic cortex, accumbens, pallidum or thalamus) might perturb the circuit dynamics in a way that results in a thought disorder, the *specific* presentation of one form of the illness might be more closely linked to one "primary" disturbance than another (e.g., subiculo-accumbens dysrhythmia). For example, virtually everyone with acute schizophrenia progresses – at least to some degree – to chronic schizophrenia; in conceptualizing a circuit for acute schizophrenia, we must consider how this circuit could change over time to account for the affective blunting and cognitive decline that characterize the residual phase of schizophrenia. We know that *something* changes over time in the brains of these patients – somewhere within this circuitry, progressive degeneration results in drastic and predictable changes in symptoms. Some anatomical signs are evident – ventricular enlargement, a loss of D2 receptors, perhaps volume loss in periventricular structures or frontal lobes. Different schizophrenic subtypes must also be accommodated by this same circuitry. What are the differences in circuit dysfunction between paranoid and catatonic forms of schizophrenia? What changes within the circuitry would bias an individual toward positive or negative symptoms? Could dysfunction within one portion of the circuitry result in schizophrenic "spectrum" disorders, including delusional disorder or schizotypal personality disorder?

Perhaps more important, can we use this circuit model in predicting therapeutic responses? For example, what types of circuit disturbances would predict responsiveness or nonresponsiveness to traditional antidopaminergic neuroleptics versus such mixed dopamine/serotonin antagonists as clozapine or even glutamatergic compounds? Is there a way to dissociate symptoms that reflect D1 versus D2 dopamine receptor disturbances based on the different roles of these receptor subtypes in the proposed circuitry? Given our progress in imaging resolution and the analysis of CSPT circuitry (London et al. 1990; Wu et al. 1990), we may soon be able to identify groups of schizophrenic patients with distinct patterns of CSPT metabolism. One utility of a model like Gray's is that it might predict a priori where within these structures we should begin to look to answer some of the above questions.

As we push these models forward, it is also important to remember that CSPT circuitry is not the "schizophrenia circuit." Indeed, this circuitry has remained more or less intact for 250 million years in mammals (MacLean 1986), most of whom were not schizophrenic. The brain has used this circuitry for disorders other than schizophrenia, and the same circuit dynamics that contribute to schizophrenic psychopathology must contribute to cognitive and affective symptoms in other forms of psychiatric illness. Some CSPT disturbances have been proposed for depression, mania (Swerdlow & Koob 1987a), obsessive compulsive disorder (Baxter et al. 1987; Rappaport & Wise 1988), aphasias (Crosson 1985), stuttering and vocal tics (Fisher et al. 1986) and Tourette's disorder (Robertson 1989), and this circuitry is believed to be critical in stimulant-induced affective changes (London et al. 1990). In fact, the association between a failure of "initiation" behavior and CSPT dysfunction might have first appeared in relation to aphasias of "Marie's quadrilateral space" (Marie 1906). In the long run, it may not be to our "advantage" to set aside these disorders and their distinct clinical presentations when we seek to understand CSPT dysfunction in schizophrenia, for surely, it's all the same brain.

The animal and human studies of latent inhibition (LI) and PREE add important support to the psychological models offered in this target article. Cross-species measurements of this type are valuable, as they allow a mechanistic, anatomical, and pharmacological dissection of aberrant human behaviors through the use of parallel animal models. We have previously described a model of abnormal information processing in schizophrenia, using electroencephalographic, electromyographic, or whole body measures of the acoustic startle reflex (Swerdlow et al. 1988). Schizophrenic patients do not exhibit the normal inhibition of their startle when the startling stimulus is preceded 60–120 msec earlier by a weak acoustic prepulse. This failure of sensorimotor gating – termed "prepulse inhibition" (PPI) – correlates with other measures of cognitive disturbances in these patients, including Wisconsin Card Sort errors (Braff et al. 1989).

This startle model is particularly suited to anatomical and pharmacological analysis; such studies yield findings that are consistent with much of the circuitry discussed by Gray et al. Deficient PPI can be produced experimentally in rats using drugs that increase brain dopamine (DA) activity: Low doses of the DA agonist apomorphine (APO) disrupt PPI in rats that are surgically altered to have "supersensitive" DA receptors in the nucleus accumbens (NAC; Swerdlow et al. 1986), whereas higher doses of DA agonists disrupt PPI in unoperated rats, and these effects are reversed by D2 (but not D1) DA antagonists (Swerdlow et al. 1990d) and by depletion of DA from the NAC (Swerdlow et al. 1990a). Thus, overactivity of NAC DA may be a substrate for the loss of sensorimotor gating in rats.

According to our model (Swerdlow & Koob 1987a) and that of Gray et al., behavioral or cognitive deficits that result from

excessive activity of NAC DA should be reversed by increases in GABA activity in the ventral pallidum (VP). Consistent with this, decreases in PPI that follow direct infusion of DA into the NAC (Swerdlow et al. 1990b) can be reversed by infusion of the GABA agonist muscimol into the VP (Swerdlow et al. 1990c). Also consistent with these models, these PPI deficits can be reproduced by VP infusions of the GABA antagonist picrotoxin (Swerdlow 1990c). CSPT circuit elements "upstream" from the NAC are also critical substrates of PPI: Infusion of carbachol into the hippocampus – a treatment that increases NAC glutamate release via subiculo-accumbens efferents (Mogenson & Nielson 1984) – disrupts PPI in rats, and this loss of gating is not reversed by DA receptor antagonists (Swerdlow et al. 1990e). As mentioned earlier, CSPT dysfunction is not unique to schizophrenia; our preliminary findings indicate that there is a significant loss of PPI in patients with Huntington's disease (manuscript in preparation). The advantages of the startle model have been discussed at length elsewhere (Braff & Geyer 1990; Swerdlow et al. 1988). Most relevant to the present issue, this model provides direct support for the anatomy and neurochemistry at three levels of the Gray circuit – the hippocampus, NAC and VP – and suggests that disturbances at any of these levels might account for information processing deficits in schizophrenia.

In summary, in their synthesis of psychological and neurological models, Gray et al. have helped put the "psych" back into the neuropsychology of schizophrenia. The neural model remains organized around motor function, whereas the psychological model remains founded in cognitive constructs, and we thus await a true union of these models. I have discussed some future considerations for this model – including the need to accommodate the clinical heterogeneity of schizophrenia within the scope of these circuit designs, the potential use of these models in predicting therapeutic approaches, and their importance for understanding other neuro- and psychopathologies. These models will be scrutinized and modified to accommodate new data, and new forms of cross validation (e.g., computer modelling of neural circuit dynamics and PET measures of circuit properties) will be important in this process. Although Gray et al. focus on subiculo- and amygdalo-accumbens dysfunction in acute schizophrenia, their discussion emphasizes the contribution of multiple levels of CSPT circuitry to the psycho- and physiopathology of this illness. Ultimately, this emphasis on dynamic interactions in CSPT circuitry is critical: As the authors conclude, it would be "otiose" to speculate on a "primary" causal lesion in schizophrenia. More than otiose, the notion that a single "hole" could be causal to the wide array of schizophrenic pathologies or that such a lesion – independent of other cascading CSPT changes – could cause psychosis contradicts 50 years of data supporting integrated limbic function. We should embrace the union of psychological and neural circuit models of schizophrenia, and throw the "hole" thing out.

Positive and negative symptoms, the hippocampus and P3

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The main contribution of the model proposed by Gray et al. is that it offers suggestions for the integration of two theories of the mechanism of schizophrenia that have been current for some time, based on hippocampal dysfunction and dopaminergic hyperactivity. The possibility of integration, however, should not immediately lead, without further examination, to the idea that the two dysfunctions have the same implications. Accepting that dopaminergic hyperactivity is reasonably associated with positive symptomatology, this commentary will examine the possible associations of hippocampal dysfunction.

The notion of hippocampal dysfunction has as one of its sources the suggestion that this may result from early damage *in utero* possibly because of the structure's vulnerability to anoxic insult. (Mednick 1970). More recent work backs this up; for example, Bogerts (1989) suggests that limbic pathology may already be present in early childhood; and Suddath et al. (1990), in providing evidence of smaller hippocampi in monozygotic twins discordant for schizophrenia, suggest (p. 793) that "some subtle failure of development" may explain the findings. It is hence possible to think of hippocampal dysfunction as underlying problems in the developing schizophrenic and hence possibly process aspects or negative aspects of the disorder.

Gray et al. are ambiguous about whether their theory is intended to apply to positive (Type 1) acute schizophrenic patients or to patients with positive symptoms. The issue is not trivial; Crow (1980b), for instance, states, and I would agree with him, that "even if Type 1 and Type 2 represent different dimensions of pathology, it is apparent that they do not constitute separate diseases." Although Andreasen and Olsen (1982) originally reported negative and positive schizophrenic symptoms as being at opposite ends of a unipolar dimension, later work has largely suggested, with Crow, that negative and positive symptoms are best thought of as forming two orthogonal dimensions; at any one time a patient may then exhibit examples of both sets of symptoms. The issue of subdiagnosis needs further clarification when the latent inhibition and blocking experiments, on which the animal-human experiment link is particularly made, are looked at closely. In the Baruch et al. (1988a) experiment the acute patients were evidently showing positive symptoms, whereas the chronic group consisted of remitted schizophrenics or outpatients who were free of hallucinations and delusions *or any other major psychiatric symptom.* Patients showing negative symptoms might have been the better theoretical contrast for the acute patients. Other studies use normal subjects rated on scales of "psychosis proneness." Baruch et al. (1988b) show that performance on a latent inhibition task was impaired in subjects high on the Eysencks' (1975b) "psychoticism" scale but not significantly on Claridge & Broks's (1984) schizotypal personality (STA), or Launay & Slades's (1981) measure of tendency to experience hallucinations. Both the latter scales would be expected to be normal analogs of the acute, positive syndrome in schizophrenia, whereas the P scale does not purport to be solely a dimensional measure of schizophrenic tendency, let alone the positive symptom aspect of it. In the case of the study by Jones et al. (1990) no relation was shown between Kamin blocking and any measure of psychosis proneness and normals' performance on the task. At the moment, therefore, Gray et al.'s rather crucial animal to human study link would appear to depend on two studies of acute schizophrenics.

Failure of latent inhibition is also a feature of hippocampectomised animals (cf. Kaye & Pearce 1987), and although, as Gray et al. state, large hippocampal lesions also destroy the crucial subiculo-accumbens projection, it is perhaps worthwhile examining the extent to which the hippocampus may also be involved in other relevant measures. To do so, is to enter an area of controversy already aired in *BBS* (Verleger 1988). This issue does provide two particular points, however: (1) the view of Halgren et al. (1988), that the P3 is generated in the medial temporal lobe, including the hippocampus, and (2) the view of Donchin and Coles (1988), that P3 is involved in "context updating." Although both of these views can be subject to argument, it is worthwhile to note that context updating can very well provide the substrate for the "stored memories of regularities" demanded by Hemsley's theory. Even if the view of the function of the hippocampus is more that of "tuning out irrelevant stimuli or events" (Moore 1979, p. 224) (which would attune it to other views of attentional dysfunctions in schizophrenia), it perhaps fits better with the original view of the

eliciting conditions for P3 by Sutton et al. (1965). It thus becomes important in this context to examine studies of P3 in schizophrenics. Pritchard (1986), reviewing the findings, which generally suggest that a smaller P3 to infrequent target stimuli is found in schizophrenics than in normals, suggests the conclusion that the "LPC [late positive complex] attenuation associated with schizophrenia may be more a trait marker of the negative schizophrenic deficit condition." More recently Pfefferbaum et al. (1989) have shown that the amplitude of P3 correlated negatively with a measure of negative symptoms in schizophrenics.

Therefore, there is a problem: a measure that has some relation to the attentional disturbance shown in schizophrenics and for which there is some presumptive evidence that it is associated with the hippocampus, an area that is implicated in the Gray et al. model, may be associated with *the more process and negative* aspect of schizophrenia.

Having thus thrown up some subdiagnostic problems raised by the model, may I at least add a piece of potentially relevant data? In 1960 I suggested that the slow reaction time of schizophrenics was not a continuous function but exhibited time quanta of 100 msec, possibly because of cortico-thalamic reverberations (Venables 1960). Could this relate to points 6 and 8 of the model?

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The accumbens–substantia nigra pathway, mismatch and amphetamine

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Gray et al.'s model of limbic-striatal interactions is both appealing and convincing, but it has several problems: (1) It is not clear why joint operation of the accumbens and caudate systems is necessary, nor what is represented by the activity of the former during the running of a particular step (which is represented by the activity of the caudate system). It appears that the accumbens system is active simultaneously with the caudate system only in order to send a match message at the end of each step and to initiate the next step. (2) How does step termination, which occurs in the accumbens system, terminate steps in the caudate system? (3) Inhibition of striatal activity at each termination of loop III is cumbersome; such a process should interfere with the smooth running of the program.

I suggest that the model's circuitry be supplemented with the inhibitory accumbens-substantia nigra (SN) projection (which appears in Figure 10 but is not given any role) as follows:

Step initiation – Following the activation of accumbens cells by amygdala, concomitantly with the activation of dorso-medial thalamus (and the ensuing activation of prefrontal cortex > sensorimotor cortex (SMC) > caudate putamen, CP), SN is inhibited via the accumbens-SN pathway, decreasing DA input to CP. On this background, the excitatory input from SMC into the CP activates caudate loop II without the interfering inhibitory DA input from SN.

Step – Excitatory cortical input to accumbens (loop II) leads to SN inhibition as above. Thus, accumbens loop II inhibits caudate loop III, so that during the step, only caudate loops I and II are active. This ensures that the program in the caudate runs smoothly, without interruption by inhibitory DA input at each termination of loop III; it also explains why a joint operation of the accumbens and caudate systems is necessary. Loop III becomes operative only when there is a need to switch ongoing activity, i.e., following step termination.

Step termination – Following the subicular inhibition of accumbens cells, inhibition of SN is removed, allowing increased DA input into the CP, and thus inhibiting CP activity, or allowing it to switch. This explains how step termination is transferred from the accumbens to the caudate system.

Another question is what neural mechanisms determine whether glutamatergic input to the accumbens is inhibitory, i.e., from subiculum (via local DA release), or excitatory, i.e., from amygdala, cortex, and presumably from subiculum in response to novelty (since it disinhibits PPN). Possibly, excitation and inhibition are produced by high and low concentrations of glutamate, respectively (Cheramy et al. 1986, target article sect. 10, para. 2; sect. 9, para. 17). This mechanism would not explain the differences between excitatory inputs from subiculum and cortex/amygdala, however, unless one postulates that these projections are differentially distributed to discrete subpopulations of accumbens neurons with different projection targets. This would complicate the model, but it would also bring it closer to the contemporary views of DA system heterogeneity. Finally, it is worth mentioning that Gray et al.'s basic postulate, that DA input is inhibitory, may need to be revised (Albin et al. 1989).

The hippocampus-subiculum projection also subserves responses to the novel or the unexpected. As someone whose view of the hippocampal function has been shaped by Gray's (1982a) model, I find the present treatment of the "mismatch" message (sect. 8, para. 6–8; sect. 9, para. 14–17) both insufficient and surprising. In the 1982 model, the subicular comparator assumes behavioral control *only* when it detects a *mismatch* between expected and actual events (p. 264). Gray's rationale for this assumption was very convincing: "We know that a rat without a hippocampus . . . runs (in an alley for food reward) just as efficiently as an intact animal. We must suppose therefore, that the hippocampus is not controlling this behavior; it is just checking" (p. 266). In the present model, the centrality of the mismatch detection is lost; the major function now is generating a match signal at the end of *each* step in the motor program. One obvious implication of this position, which is difficult to reconcile with Gray's earlier arguments as well as with empirical data, is that hippocampal lesions should disrupt animals' performance in any learning task. I have proposed elsewhere (Weiner 1990) that the function of the subiculum-accumbens projection is to control the switching mechanism of the accumbens only under conditions of mismatch. More specifically and very briefly, on the basis of mismatch analysis the hippocampal comparator selects one of two behavioral alternatives, changes behavior or continues behavior as before in spite of the mismatch, and generates signals for switching or not switching of behavior, respectively, for the accumbens.

Turning to behavioral experiments (sect. 4), Gray et al.'s rationale for focusing on latent inhibition, blocking and the PREE ("each of these phenomena . . . " sect. 4, para. 2) strikes me as applicable to *any* learning paradigm, and thus as meaningless. If we are to benefit from animal research in modelling cognitive abnormalities of schizophrenia, a fine grained analysis of the behavioral mechanisms governing each learning task and of their alterations by amphetamine and other relevant manipulations is crucial. As a relevant example, hippocampal lesions and amphetamine do not always have the same consequences, as predicted by Gray et al. (sect. 4, para. 8), e.g., multi-trial PREE is disrupted by hippocampal lesions, but not by amphetamine (Feldon et al. 1989; Feldon & Weiner 1989), and discrimination reversal is impaired by the former but facilitated by the latter (Weiner et al. 1986a; 1986b; 1987a; Weiner & Feldon 1986). These differences should be very meaningful for Gray et al.'s model, yet they are overlooked.

Finally, amphetamine (AMPH)-induced release of DA by no means "disrupts the running of all steps in all motor programs indiscriminately" (sect. 10, para. 2). First, at low, hyperactivity-inducing doses, DA release is coupled to impulse flow, which,

although enhanced, remains relatively unaltered (Geyer et al. 1987; Kuczenski 1983). Second, in behavioral tests, low doses do not necessarily produce impairments; in fact, they may facilitate learning (e.g., Mithani et al. 1986; Robbins et al. 1983; Weiner et al. 1986a; 1986b; 1987a; Weiner & Feldon 1986). Even at stereotypy producing doses, which activate striatal DA receptors in an impulse flow independent manner (Geyer et al. 1987; Kuczenski 1983), animals are capable of performing, for example, operant responses. And, as noted by Gray et al., latent inhibition is disrupted by low but *not* by high doses of AMPH (Weiner et al. 1978).

In short, AMPH-induced release of DA yields a complex pattern of behavioral alterations that are highly specific to the situation tested. In fact, the behavioral effects of this drug are modulated by changes in relatively subtle experimental parameters, such as the intertrial interval (Feldon et al. 1989; Feldon & Weiner 1989). Indeed, if the influence of AMPH were indiscriminate, as Gray et al. maintain, this drug would be of no value as an animal model of schizophrenia. After all, the deficits observed in schizophrenia, although varied and complex, cannot be described as an indiscriminate disruption of all steps in all motor programs.

The neuropsychology of schizophrenia: In step but not in time

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Gray et al. propose that the septohippocampal system (SHS) monitors the sensory consequences of individual motor steps programmed by the striatal motor system (SMS). Switching from one motor step to the next requires a subicular outflow to the nucleus accumbens, which is both topographically *and temporally* appropriate in order to signal that the SHS has monitored successful completion of the previous step. Positive schizophrenic symptoms arise from disruption of this subicular signal. The target article concentrates on factors that determine the topography of the accumbens' response to the subiculum, but, although it briefly attributes synchronisation of the subicular and accumbens activities to the SHS theta rhythm, it neglects the consequences of disrupting this timing mechanism. The timing of the subicular signal is critical for the hypothesis: Any signal at the wrong time is the wrong signal. Therefore, schizophrenic symptoms may arise from disruption of the SHS EEG theta rhythm, so that the functions of the SHS and SMS are not in time. This is the focus of this commentary.

Gray et al. confine their model to schizophrenia. Schizophrenic symptoms or even clinical pictures very like schizophrenia can, however, arise in diverse chronic organic disorders (Davison 1983) or in affective (Carpenter et al. 1973) or acute organic psychoses (see Horvath et al. 1989). Parsimony requires explanation of the phenomenological overlap between psychotic disorders by abnormal activity in a final common pathway (Davison 1983). This explanation is attempted here.

The possibility that disrupting human SHS EEG rhythms causes psychotic symptoms gains face validity from the associations of schizophrenia-like psychoses with temporal lobe epilepsy (Perez et al. 1985; Slater et al. 1963), abnormal septal spike activity (see Heath & Walker 1985) and medial septal structural abnormalities (Lewis & Mezey 1985). Although structural and functional analogies between the human and subprimate SHS are uncertain, each of these brain abnormalities, if produced experimentally in rodents, could disrupt hippocampal theta (see Chapter 4 in Gray 1982a). These clinical associations, however, do not prove a causal role for abnormal hippocampal EEG rhythms in producing psychotic symptoms. Testing the causal model requires a means of disrupting human EEG rhythms experimentally, to allow controlled studies of the mental state and behaviour.

Studies on centrally acting anticholinergic drugs fulfil the requirements set out above. In subprimate species, these drugs disrupt low-frequency theta during immobility, but spare the higher frequencies associated with movement (see Vanderwolf, 1988, for review). In man, similar relations between movement and scalp EEG alpha frequencies are found after biperidine treatment (Westphal et al. 1987). Hence anticholinergics disrupt a human EEG rhythm in a manner analogous to their effects on subprimate hippocampal theta.

Psychological effects of anticholinergics pertinent to the target article have been studied in detail in man. Low-doses weaken memory, impair attention, and can even induce simple auditory hallucinations and mild loosening of associations (Warburton 1989). In particular, scopolamine may affect the "pigeonholing" process fundamental to Hemsley's account of schizophrenic psychopathology (Dunne & Hartley 1986; cf. target article, sect. 2). In high doses, anticholinergics can cause acute organic psychosis with marked loosening of associations, complex hallucinations, loss of insight, and transient paranoid symptoms (Ketchum et al. 1973). This picture is usually readily differentiated from schizophrenia by drowsiness and an excess of visual hallucinations (which occurs also in the psychosis due to amphetamines, Bell 1965). Occasionally, however, anticholinergics can precipitate schizophrenia in predisposed individuals (Trend et al. 1989).

Anticholinergic drugs, then, have psychological actions directly in line with the target article's model of schizophrenia. Recall, however, that anticholinergics disrupt EEG rhythms associated with immobility and spare those during movement. At first sight, this does not fit with the target article's model for controlling motor programmes. But a reformulation of Gray's (1982) hypothesis of subprimate hippocampal theta functions (*quod vide*) can resolve this profitably. The behavioural correlates of Gray's "control" and "checking" theta modes correspond to the distinction between controlled and automatic attentional processing (target article, sect. 8, para. 7). Hence control mode theta may participate in controlled attentional processing and checking mode theta in automatic processing. Given the view that exercising selective attention is a form of cognitive action plan (sect. 2, para. 9), this reformulation of theta function renders the selective effects of anticholinergics on immobility-related EEG rhythms compatible with the target article's model for controlling motor programmes (and with numerous data relating atropine-sensitive theta to sensory stimulation; see review by Bland 1986).

The evidence presented above has shown rather generally that disrupting limbic EEG rhythms may contribute to producing psychotic symptoms. But Gray et al. (sect. 9, para. 8) predict a precise one-to-one relationship between motor steps and SHS theta waves. Schallert et al. (1980) tested this hypothesis using split-screen slow-motion video analyses of behaviour and EEG in rats. Controls showed momentary immobility between different behaviours associated with low-frequency theta. Atropine abolished the low-frequency theta and caused thigmotaxic stereotypies. These results fit the prediction (sect. 9, para. 11) that without a subicular input to the accumbens the SMS would repeat the same pattern of activity. They also strongly support the view that low-frequency control mode theta waves participate in controlling motor activity; but they also suggest that this theta controls shifts *between* motor programmes (visible as stereotypies) rather than steps *within* them. The majority of theta waves, occurring during each motor stereotypy, were high-frequency checking mode. This type of theta is disrupted by the serotonin-depleting drug parachlorophenylalanine and by phencyclidine (see review by Vanderwolf 1988). Both these drugs are relevant here: Hippocampal serotonin depletion reduces latent inhibition (sect. 4, para. 11) and phencyclidine can

produce acute psychotic states very like acute schizophrenia (see Jaffe 1989). This limited evidence therefore suggests that disrupting checking mode theta can also contribute to producing psychotic symptoms.

In summary, drugs or brain disorders that may disrupt the SHS theta rhythm in subprimates can give rise to psychotic symptoms in man. The possibility that psychotic symptoms are the result of disruption of SHS EEG rhythms desynchronising the activities of the SHS and the SMS broadens the scope of the model of schizophrenia proposed by Gray et al. This is not to imply that schizophrenia is a form of atropine psychosis or seizure disorder, nor, conversely, that any drug or brain disorder which disrupts SHS EEG rhythms will cause psychosis. But the arguments developed here narrow attention to the timing component of the functional linkage between the SHS and the SMS as a plausible candidate for the final common pathway where various brain abnormalities may produce psychotic symptoms. Extending the model proposed by Gray et al. to integrate detailed electrophysiological observations with the numerous data they have already assembled from other disciplines will permit more stringent tests of their hypothesis in both experimental and clinical settings.

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Authors' Response

Schiz bits: Misses, mysteries and hits

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1. Points of agreement

Before we embark on the serious business of answering the many important questions raised by the commentaries, we note with gratitude – not to say relief – the various commendations that the target article received. We accept that these must in the main reflect the customary courtesy of contributors to **BBS**. It is nonetheless worth picking out those features of the model that were seen as its strong points. These were: Its breadth and capacity to integrate across different levels of observation and theory (neuroanatomical, neurochemical, behavioural, cognitive psychological, and clinical) (**Crusio, Dawson & Hazlett, Elkins & Cromwell, Frith, Hoffman, Lubow, Nuechterlein & Green**); its relatively high degree of specificity (Elkins & Cromwell, **Jansen & Faull, Manschrek & Maher**) – though Frith found it more specific than is warranted by current knowledge, and **Sarter** warns against "hodological phrenology"; its reliance for clinical evidence on paradigms in which the predicted, and found, effect is a *superiority* of schizophrenic performance (Elkins & Cromwell); and its testability and heuristic value (**Early & Haller**, Elkins & Cromwell, Jansen & Faull, Manschrek & Maher, **Pilowsky & Murray, Pisa & Cleghorn, Spohn**). We are pleased that this last point – which for us is cardinal – is so widely agreed on.

Also widely agreed – indeed, *nemine contradicente* – is that it is reasonable to search for an understanding of schizophrenia in the brain, a consensus that would have been unthinkable just a few years ago as **Frith** points out. The only major criticism on this score was that we have not gone far enough: We appear to have still left a "ghost in the machine," though this seems to be Frith's (1987) ghost rather than ours. Only **Claridge & Beech** express a general doubt about the quality of the neuropathological data on the schizophrenic brain, which have been an important element in picking out the brain structures emphasised in our model; they complain about "the almost embarrassing *variety*" of relevant evidence. We were quite selective in our reliance on neuropathological data, choosing only findings that were relatively well replicated; indeed, we received some criticism for leaving out of our model certain regions that have sometimes been reported to be abnormal in the brains of schizophrenics – e.g., the corpus callosum or regions around the third ventricle (**Raine & Cannon, Sandyk & Kay**).

Several commentators liked our focus on a brain *system* or *circuit* rather than a discrete lesion or "hole" (**Swerdlow**). This permits one to attempt to explain particular features of the schizophrenic syndrome, or the variability and heterogeneity so characteristic of this syndrome (**Manschrek & Maher, Pisa & Cleghorn, Pilowsky & Murray**), in terms of separate and discrete but related malfunctions in the overall circuit (**Cools & Ellenbroek, Crusio, Swerdlow**). But we endorse Swerdlow's comment that this is not a "schizophrenic circuit"; rather, it is one that "has remained more-or less intact for 250 million years in mammals (MacLean 1986), most of whom were not schizophrenics." We are particularly encouraged by the excellent agreement between the results obtained by Swerdlow and his collaborators using their model of prepulse inhibition (Swerdlow & Koob 1987a) and our own, described in the target articles. As Swerdlow says, their results provide "direct support for the anatomy and neurochemistry at three levels of the Gray et al. circuit – the hippocampus, n. accumbens and ventral pallidum – and suggest that disturbances at any of these levels might account for information processing deficits in schizophrenia." Rather than summarise these results further, we would simply urge everyone to read Swerdlow's commentary.

Hardly more disagreement was provoked by the premise, central to our approach, that animal models of at least some critical features of schizophrenia are possible and useful. **Claridge & Beech** were again alone in clearly disagreeing with this approach, though **Elkins & Cromwell** and **Raine & Cannon** point to some possible hazards and limitations; **Frith, Goldberg, Lubow** and **Swerdlow**, in contrast, positively welcomed it. A particular hazard of animal models is said to be the focus this may give to

Table 1. *Outline of author's response*

Topic	Commentators
1. Points of agreement.	**Claridge & Beech, Cools & Ellenbroek, Crusio, Dawson & Hazlett, Early & Haller, Elkins & Cromwell, Frith, Goldberg, Hoffman, Janowsky, Jansen & Faull, Lubow, Manschreck & Maher, Neuchterlein & Green, Oke & Adams, Patterson, Pilowsky & Murray, Pisa & Cleghorn, Raine & Cannon, Sandyk & Kay, Sarter, Spohn, Swerdlow.**
2. Of what do we have a model?	
a) Schizophrenia or psychosis?	**Hestenes, Ingraham, Joseph, Manschreck & Maher, Sandyk & Kay, Williams.**
b) Limitation of the model to positive symptoms.	**Elkins & Cromwell, Frith, Ingraham, Jansen & Faull, Oke & Adams, Swerdlow.**
3. The relationship of loss of latent inhibition to positive symptoms.	**Dougherty et al., Hoffman, Manschreck & Maher, Nuechterlein & Green, Oades, Raine & Cannon, Sandyk & Kay, Spohn, Steinhauer & Zubin, Venables.**
4. The relationship of loss of inhibition to dopaminergic activity.	**Neuchterlein & Green, Oades.**
5. The excess dopamine hypothesis.	**Dougherty et al., Early & Haller, Hoffman, Ingraham, Jansen & Faull, Nuechterlein & Green, Pilowsky & Murray.**
6. Limitation of the model to positive symptoms: reprise.	**Elkins & Cromwell, Frith, Manschreck & Maher, Patterson, Raine & Cannon, Sandyk & Kay, Spohn.**
7. The relationship between structural and functional abnormalities.	**Dougherty et al., Nuechterlein & Green, Oades, Pilowsky & Murray, Raine & Cannon, Spohn, Venables.**
8. The relationship between positive and negative symptoms.	**Crusio, Elkins & Cromwell, Manschreck & Maher, Nuechterlein & Green, Pilowsky & Murray, Salzinger, Sandyk & Kay, Sarter, Swerdlow, Venables.**
9. State or trait?	**Elkins & Cromwell, Lubow, Raine & Cannon, Venables.**
10. Latent inhibition and habituation.	**Dawson & Hazlett, Frith, Gewirtz, Lubow, Schmajuk & DiCarlo.**
11. Selective attention or learning about context?	**Dawson & Hazlett, Dougherty et al., Elkins & Cromwell, Frith, Gewirtz, Harrow & Silverstein, Hestenes, Lubow, Oades, Patterson, Salzinger, Schmajuk & DiCarlo, Spohn, Stevens & Gold, Venables.**
12. Controlled vs. automatic processing.	**Gewirtz, Lubow, Nuechterlein & Green, Oades.**
13. The plausibility of the model in relationship to symptom formation.	**Harrow & Silverstein, Hoffman, Patterson, Salzinger, Stevens & Gold, Swerdlow.**
14. Hemispheric lateralisation.	**Elkins & Cromwell, Goldberg, Raine & Cannon, Spohn.**
15. Input dysfunction.	**Elkins & Cromwell, Oades, Patterson.**
16. Motor programming.	**Crider, Early & Haller, Hestenes, Oke & Adams, Pilowsky & Murray, Stevens & Gold, Swerdlow.**
17. The model for motor programming.	**Carlsson & Carlsson, Cools & Ellenbroek, Crider, Dougherty et al., Frith, Hoffman, Oke & Adams, Patterson, Pisa & Cleghorn, Stevens & Gold, Swerdlow, Venables, Weiner, Williams.**
18. The hippocampal formation.	**Crusio, Early & Haller, Oades, Pisa & Cleghorn, Schmajuk & DiCarlo, Williams.**
19. The subiculo-accumbens projection.	**Carlsson & Carlsson, Early & Haller, Joseph, Oades, Pisa & Cleghorn, Schmajuk & DiCarlo, Stevens & Gold, Weiner.**
20. The neocortex.	**Dawson & Hazlett, Frith, Goldberg, Hoffman, Pilowsky & Murray, Raine & Cannon, Sandyk & Kay, Spohn, Swerdlow.**
21. Psychotomimetic drugs.	**Hoffman, Jansen & Faull, Williams.**
22. Conclusion.	**Weiner.**

'relatively low-level brain structures' (Claridge & Beech), with a consequent under-emphasis on "the potentially critical role of cortical abnormalities in schizophrenic symptomatology" (**Raine & Cannon**). But we see no way in which the structures in the limbic system and basal ganglia referred to in our model can be described, even relatively, as "low-level"; and other commentators, especially **Patterson,** agree with the importance we attach to such subcortical structures. Furthermore, although it is true that the human neocortex is relatively much larger than it is in other animals (Raine & Cannon), there is no reason (as stressed by Goldberg) to suppose that cortical functions are essentially different in animals and man; and our model does, in any case, attribute important roles to neocortex, both temporal and prefrontal. Raine & Cannon point out that reliance on animal research is likely to lead to difficulties in accounting for hemispheric asymmetries (we agree: see the section on hemispheric lateralisation, below), and to similar difficulties in dealing with language, which is "critical for the expression of schizo-

phrenia." In contrast, Goldberg welcomes the "evolutionary continuity" of our treatment of the latter topic and indicates how language function may have grown in the human left hemisphere out of more basic differences in the cognitive functions of the two hemispheres in nonhuman animals; **Oke & Adams** find acceptable our treatment of language as a special form of motor programming (though they question some of the anatomical details).

Thus, with these exceptions, the commentators are prepared to accept the importance in schizophrenia, not merely of the brain in general terms, but also of those particular brain structures (though not necessarily with the same emphases) on which our model focuses.

2. Of what do we have a model?

There is, then, overall agreement that the most general assumptions underlying our model – that schizophrenia is a brain dysfunction, that post mortem material provides clues to the relevant neuropathology, that neuropsychological models are useful, and that data obtained with animals are relevant to their construction – are acceptable. There is confusion, however, about *what* exactly we are modelling. This is not surprising; the confusion stems, at least in part, from the way we have set about constructing the model and from current limitations on the relevant data base. The roles played by these two factors will become apparent as we discuss particular issues raised by the commentators. Two closely related questions came up repeatedly: The first concerns whether we have modelled something broader (viz., psychosis) than schizophrenia; the second concerns whether we have modelled something narrower (viz., only the positive symptoms of schizophrenia). The answers to these two questions are similarly closely related; we deal with them in turn.

(a) Schizophrenia or psychosis? Are we modelling psychosis rather than schizophrenia, **Ingraham, Manschrek & Maher, Sandyk & Kay,** and **Williams** ask. As these commentators point out, neither positive psychotic symptoms nor dopaminergic overactivity is uniquely associated with schizophrenia. Thus, the part of our theory that stems from the overattention caused by dopaminergic overactivity (as, e.g., the lost of latent inhibition, LI, or the Kamin blocking effect, KE, after amphetamine administration) may in principle apply equally well to, for example, mania (**Hestenes**). In practice, however, we so far have relevant data only for acute and chronic schizophrenics (Baruch et al. 1988a; N. S. Gray unpublished data; Jones 1989), not for manic patients. Thus, evidence about whether the latter group (a *minority* of whom hallucinate), like acute schizophrenics, fail to show LI or KE is critical for determining the applicability of this part of our model to psychosis in general. From the effects of amphetamine on LI and KE (for references, see target article), it is possible that manic patients will indeed, in these respects, resemble acute schizophrenics; but until the data are obtained, it would be premature to extend the model in this way.

Notice, however, that the argument from the effects of amphetamine is not the only route to the prediction of loss of LI and KE in schizophrenia. We relied also on evidence that, in animals, these effects are abolished by damage to the hippocampal formation (references in target article), together with post mortem data indicating damage to this and related temporal lobe structures in the schizophrenic brain. We are not aware of evidence that would permit this line of argument to be applied to other cases of psychotic behaviour, except for that seen in temporal lobe epilepsy (its significance for our model having been pointed out by **Williams**); nor are we aware of evidence implicating dopaminergic overactivity in the latter condition. Thus, the use of both arguments in combination makes our model more clearly applicable to the psychotic behaviour of schizophrenia than to any other kind of psychotic behaviour; and the key experiments we have used so far to test the model clinically are indeed based on both arguments.

(b) Limitation of the model to positive symptoms. The second criticism noted above was voiced by **Elkins & Cromwell, Ingraham** and **Swerdlow:** It concerns the wisdom of limiting our approach, within schizophrenia, to positive symptoms (though **Jansen & Faull, Oke & Adams,** and Swerdlow see the practical advantages of such a limitation; and **Frith** is pleased to see us start from symptoms, which "have the advantage of remaining relatively well defined," rather than from diagnostic categories, which shift "back and forth with the swings of fashion"). We again acknowledge here that part of the puzzlement felt by commentators arises from the way we have constructed our model. The joint argument from dopaminergic overactivity and limbic damage, as noted above, points rather clearly to the positive symptoms of acute schizophrenia as the first phenomena to be explained; and to the initial clinical research strategy we adopted to test the model, namely, to contrast acute and chronic schizophrenics on tasks sensitive to both dopaminergic overactivity and hippocampal structural damage. Does this mean, then, that our model has nothing to say about other aspects of schizophrenia? This criticism was most forcefully put by Ingraham, who questioned whether the term "schizophrenia" should have figured in our title at all. Before we can properly address this issue, however, we must first deal with a number of other related points raised by the commentators.

3. The relation of loss of latent inhibition to positive symptoms

We chose to concentrate on the positive symptoms of acute schizophrenia because the specifically new features of our model make their clearest predictions for patients who have these symptoms at this stage of the illness. Note that this formulation is (deliberately) ambiguous as to the question, raised indirectly by many commentators (**Manschrek & Maher, Nuechterlein & Green, Raine & Cannon, Sandyk & Kay, Spohn**) and directly by **Venables,** as to whether it is "intended to apply to positive (Type 1) acute schizophrenic patients or to patients with positive symptoms." We were aware of the fact pointed out by all these commentators that positive symptoms occur in chronic as well as in acute stages of the illness; we were also aware that dopamine (DA) receptor blockade with neuroleptics is only partially successful in the control of positive symptoms. At the start of our clinical research

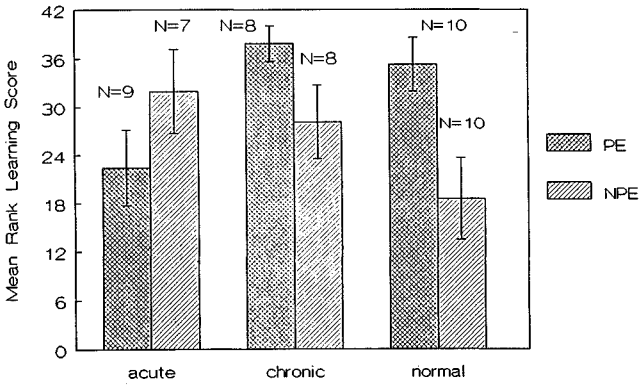

Figure 1A. The interaction between pre-exposure condition and acute vs. chronic schizophrenia. Error bars indicate standard error of the mean rank. PE = Pre-exposed. NPE = non-pre-exposed.

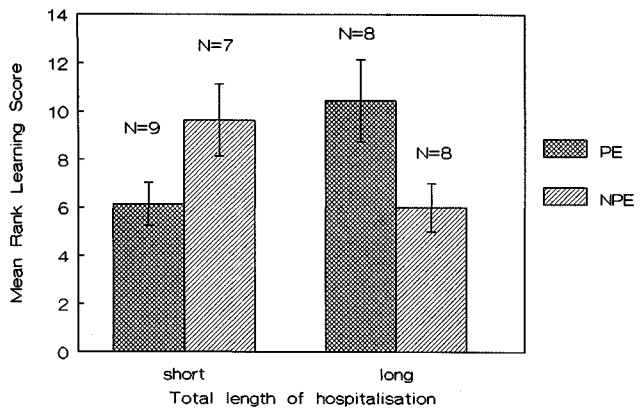

Figure 1B. The interaction between pre-exposure condition and schizophrenia, as a function of short (<20 months) vs. long (>20 months) hospitalisation. Error bars indicate standard error of the mean rank. PE = pre-exposed. NPE = non-pre-exposed.

programme, therefore, we could have equally well pursued either of the two following lines of argument (both based on the evidence that, in the rat, LI and KE are disrupted by amphetamine and that these effects are reversed by neuroleptics).

(1) We could have linked blockade of LI and KE directly to positive symptoms, supposing that, in chronic patients under long-term neuroleptic administration, the resultant DA receptor blockade was insufficient to normalise LI and KE. We could thus have predicted that loss of LI and KE would characterise patients with positive symptoms, whether in acute or chronic stages.

(2) We could have linked blockade of LI and KE directly to DA overactivity, supposing that neuroleptic administration, even when unable to control positive symptoms, normalises DA activity; we could thus have predicted that loss of LI and KE would occur only in the acute stage. The strongest prediction we could make, therefore, was that LI and KE would be absent in acute patients with positive symptoms. These predictions were indeed upheld (Baruch et al. 1988a; Jones 1989).

The results of these first studies, therefore, left it unclear whether loss of LI and KE occurs in patients with positive symptoms, in acute patients, or only in those with both these characteristics. They also left unclear the relationship between these phenomena and DA receptor blockade – uncertainties in the interpretation of the data that were pointed out by **Dougherty et al., Hoffman, Nuechterlein & Green, Oades,** and **Venables.** Fortunately, these issues have been to some extent clarified by data gathered by N. S. Gray (unpublished data) since the target article was written. She has repeated the essential features of the Baruch et al. (1988a) study of LI in acute and chronic schizophrenics with essentially the same results (normal LI in the chronic group, loss of LI in the acute sample; Figure 1A). (We draw this replication to Venables's attention, because he has rightly commented on the small size of our data base.) In the Baruch et al. study, the chronic patients had lower scores on the Brief Psychiatric Rating Scale (BPRS) than did the acute subjects. Furthermore, as emphasised by Nuechterlein & Green, dichotomising the patients on BPRS scores was at least as good a predictor of the loss of LI as chronicity. Thus, the loss of LI in the Baruch et al. (1988a) study might have been associated with either a high level of positive symptoms, or the acute stage, or both. In N. S. Gray's study, however, there were no significant differences between BPRS scores in the acute and chronic groups (the means differed by only about 10%, and both were higher than in Baruch et al.'s acute group); she also found no relationship between such scores (either total or separated into positive and negative symptoms) and the loss of LI; yet she still found the clear acute/chronic difference in LI shown in Figure 1A. In addition, she found normalisation of LI to be strongly and positively related to total length of hospitalization (Figure 1B). We can accordingly conclude that the loss of LI is associated, not with positive symptoms, but with the acute stage of the illness (i.e., in both the Baruch et al. and N. S. Gray's studies, the first two weeks of a current episode, with normalisation of LI being clear by eight weeks in the Baruch et al. study).

4. The relation of loss of latent inhibition to dopaminergic activity

Taken together, then, the results obtained by Baruch et al. (1988a) and by N. S. Gray (Figures 1A and 1B) indicate that LI is lost in the first two weeks of an acute schizophrenic illness. The most appealing interpretation of this pattern of results is that normalisation of LI is the result of neuroleptic medication; N. S. Gray's results discount any major influence of neuroleptic dose as such (an issue raised by **Neuchterlein & Green** and by **Oades**), because her chronic patients were taking higher doses than the acute ones, whereas in the Baruch et al. (1988a) study the reverse was the case. The neuroleptic medication effect is in turn most readily interpreted as reflecting DA receptor blockade. Interpretation along these lines is supported by a further finding in N. S. Gray's experiments, namely, that in normal human subjects LI is abolished by a single low (5 mg) dose of oral amphetamine. Thus, loss of LI appears to be a very sensitive index of heightened dopaminergic activity. This inference is supported by recent findings in animal experiments. Weiner et al. (1988) have demonstrated that LI is abolished in the rat by two doses of amphetamine; and Peters, Joseph & Gray (unpublished data) have been able to abolish LI with two injections of nicotine at a dose (0.4 mg/kg) that has no

effect on DA release in the dorsal striatum but elevates DA release in n. accumbens (Imperato et al. 1986). Since one or two low doses of either amphetamine or nicotine (whose effects on LI in human subjects are currently under investigation in our laboratory) do not give rise to psychotic behaviour, these psychopharmacological results are consistent with the data on schizophrenic patients in emphasising the DA-LI link rather than the link between LI and psychotic symptoms. It appears from Oades's description of measurements of DA excretion in schizophrenics tested in a KE paradigm that he finds evidence for a similar DA-KE link.

5. The excess dopamine hypothesis

This line of argument, however, runs into the well-known difficulties that surround the excess DA hypothesis of schizophrenia. These difficulties were mentioned by **Dougherty et al., Early & Haller, Hoffman,** and **Pilowsky & Murray.** In addition, **Ingraham** comments on the weaknesses of amphetamine induced conditions as a model for acute schizophrenia, pointing out the greater similarity to the paranoid state, the existence of extra symptoms (e.g., hypersexuality) that are absent in schizophrenia, and the multiple effects of this compound on transmitter systems other than the dopaminergic. Although these general problems surrounding the DA hypothesis of schizophrenia remain, it is difficult to see how any behavioural observation can be closely related both to (1) the dynamics of DA release and receptor activation and at the same time to (2) the time course of the formation and disappearance of psychotic symptoms. Our observations on LI are no exception to this rule. In the main, they fit better (as noted above) with the DA than the symptom side of the story, particularly with respect to the abolition of LI by acute amphetamine in human subjects and acute nicotine in rats, and the return of LI in chronically medicated schizophrenics who continue to display a high level of positive symptoms. On the other side of the coin, however, as pointed out by **Nuechterlein & Green,** the acute schizophrenics in the Baruch et al. (1988a) study – as well as in N. S. Gray's (unpublished data) study – were taking neuroleptics, so the loss of LI in these patients appears to be more closely related to the time course of symptomatic change produced by neuroleptics than to that of DA receptor blockade. Until the general mystery surrounding the role of DA in schizophrenia is resolved (see Pickar, 1988, for some illuminating suggestions) – and no commentator appears inclined to suppose that DA plays no role – this is probably about as clear a set of results as one can expect. We are intrigued by the suggestion (**Jansen & Faull**) that the solution to the mystery lies in the action of neuroleptics on sigma receptors coupled with that of sigma receptor ligands on DA systems. Studies of the effects of such ligands on LI and KE might pay handsome dividends.

6. Limitation of the model to positive symptoms: Reprise

Having addressed some of the issues relating to our key clinical observations – loss of LI and KE in the acute stage of schizophrenia – we now return to the criticism that we should not have limited our model to the positive symptoms that are characteristic – but by no means, as we agree, uniquely so – of this stage. Our conclusion so far is that loss of LI (and presumably of KE, though our data base for this phenomenon is as yet smaller) in acute schizophrenia reflects dopaminergic overactivity, almost certainly in n. accumbens (for reasons given in the target article and reinforced by the findings with nicotine). The relation of the loss of LI and KE to positive symptoms is, as we have seen, weakened by some of the same observations that have strengthened its relation to DA activity and acute schizophrenia. In the light of these preliminary conclusions, should our model have dealt also with negative symptoms; and can it do so?

A number of commentators spelled out the reasons we should have dealt with negative symptoms. Above all, as pointed out by **Manschrek & Maher, Raine & Cannon, Sandyk & Kay,** and **Spohn,** it is rare for schizophrenics to show only positive or negative symptoms. Thus, an explanation applicable only to the former risks missing out a central feature of the condition. **Elkins & Cromwell** go so far as to suggest that positive symptoms as such may be "peripheral rather than central to schizophrenia"; **Patterson** has a similar view of one particular positive symptom, namely, hallucinations; and Manschrek & Maher question the very categories of positive and negative symptoms, on the grounds that "these categories lump together behaviors that . . . may be quite different in their measureable properties." Although we accept the cogency of the latter point, we would point out that (as approved by **Frith**) we have focused not on the category of positive symptoms, but on an abnormality of cognitive processing that gives rise to symptoms of this kind according to the model.

7. The relation between structural and functional abnormalities

Other reasons why our neglect of negative symptoms was regarded as mistaken stem from the fact that our model supposes that there is *structural* damage in the schizophrenic brain (especially in the limbic system and the temporal lobe), and this is what results in functional overactivity in the dopaminergic innervation of the basal ganglia. As **Nuechterlein & Green** put it, "the primary dilemma is that the critical neuropathology on which the model is based is stable rather than transient in nature, but the positive symptoms of schizophrenia are often episodic rather than continuous." These commentators accept that, even given the mystery surrounding the DA hypothesis of schizophrenia (see above), the remission of positive symptoms (and the normalisation of LI) with treatment of acute episodes by neuroleptic drugs can in principle be accommodated within such a mixed structural/functional model. (We might add that there is need for far more data of the kind described by **Oades,** in which neuroleptics can be shown to reverse the behavioural effects of hippocampal damage, to substantiate this possibility, especially with such paradigms as LI and KE, which have credentials as models of the cognitive abnormalities of acute schizophrenia.) There are other features of schizophrenia, however, that are more recalcitrant to

incorporation into a mixed structural/functional model of the kind we have proposed.

First, as pointed out by many commentators (especially **Pilowsky & Murray,** but see also **Nuechterlein & Green, Raine & Cannon, Spohn,** and **Venables**), there is evidence that structural and cognitive abnormalities are present from very early life, long predating the first appearance, typically during late adolescence, of acute schizophrenia and positive symptomatology. The question therefore arises: What triggers the transformation of these predisposing factors into the functional DA overactivity that is presumed to underlie acute positive symptoms? As well as raising this question, Pilowsky & Murray offer a likely answer: continued brain development. In particular, they (and **Oades**) indicate the possible significance for our model of the observation (Benes 1989) of the "strikingly increased myelination of the subicular and pre-subicular regions" during late adolescence in normal brains. Because in our model the subiculo-accumbens pathway is given the chief burden of linking limbic pathology to DA overactivity, this is indeed an intriguing possibility.

Second, even during drug-free periods, positive symptoms show a variable course, which again leads to a question: What translates the presumed permanent structural abnormality into the transient functional one (**Dougherty et al., Nuechterlein & Green, Pilowsky & Murray, Raine & Cannon**)? One possibility lies in the conjunction of (1) clinical data indicating that relapse in schizophrenic patients is greater, the greater the degree of emotion (particularly hostile emotion) expressed by the relatives who care for them (Leff 1987), and (2) data from animal experiments demonstrating increased dopaminergic transmission in response to stress (see Gray 1982a, p. 422, for references). Conceivably an altered dopaminergic response to stress (Dougherty et al.), consequent on the postulated structurally abnormal limbic input to the basal ganglia, mediates the effects of expressed emotion on schizophrenic relapse.

Third, both **Pilowsky & Murray** and **Raine & Cannon** cite evidence that structural abnormalities in the schizophrenic brain are associated more closely with negative than with positive symptoms; **Venables** cites similar evidence for the amplitude of the P300 scalp potential, which is perhaps an index of structural damage in the hippocampal formation (Halgren et al. 1980). We see no reason to dispute this evidence; indeed, as we shall see, it is readily compatible with a slightly extended version of our model. But it is this evidence, above all, that convinces us that it was indeed unwise not to pay more attention in the target article to the relation between positive and negative symptoms. Clearly, if (as we postulate) structural abnormalities give rise to the functional changes that underlie the positive symptoms of acute schizophrenia, and if structural abnormalities are closely related to negative symptoms, then our account leaves out a vital link if it says nothing about the relationship between positive and negative symptoms and how this relationship reflects both structural and functional factors. We shall attempt to fill this gap here.

Before doing so, however, we note that, if **Pilowsky & Murray** are correct in proposing that there are separate "chronic" and "relapsing and remitting" forms of schizophrenia, of which only the former is associated with structural abnormalities, then the enterprise on which we are about to engage is misconceived; for, in their view, positive symptoms (which they attribute to both these forms of schizophrenia) would have no necessary link to structural abnormalities of the kind on which our model rests. But if their view is correct, we wonder why Baruch et al. (1988a) were able to see identical differences in LI in both a cross-sectional design, contrasting separate groups of acute and chronic schizophrenics, and a longitudinal design, contrasting the same group of schizophrenics tested at two and eight weeks after the onset of the current episode.

8. The relationship between positive and negative symptoms

One way to relate the distinction between positive and negative symptoms to the further distinction between structural (limbic) and functional (dopaminergic) abnormalities was adumbrated in the commentary by **Nuechterlein & Green.** It takes the familiar form of a vulnerability/stressor model, in which the structural abnormalities provide the vulnerability factor. Several commentaries raise the question of the origin of these abnormalities. We continue to believe that, although the question of aetiology is clearly of fundamental importance (**Manschrek & Maher**), our model is in its essentials unaffected by its resolution: Whether the origin of the neuropathology of the schizophrenic brain lies in genetic factors (**Crusio, Elkins & Cromwell**), complications of pregnancy and birth (**Crusio, Venables**), neurodevelopmental factors (**Pilowsky & Murray**), an interaction between perinatal and genetic factors (De Lisi et al. 1988), or progressive degeneration (a possibility that only **Swerdlow** mentions), we would still need to seek a mechanistic account of the way the resulting faulty brain gives rise to faulty behaviour.

Animal data provide an intriguing illustration of the way developmental factors may come to determine adult attentional performance. Male rats that are nonhandled throughout infancy (i.e., entirely undisturbed from birth to weaning on Day 22) fail to exhibit either LI or the partial reinforcement extinction effect (PREE) as adults (Weiner et al. 1985; 1987d; 1987e; 1990). Remarkably, this behavioral deficit is reversed by neuroleptic treatment (Feldon & Weiner 1988). These results suggest that infantile nonhandling leads to a DA-mediated deficit that mimics the deficit induced by amphetamine in normal adult rats. It is interesting to note that nonhandling produces alterations in the neural organisation and development of the hippocampus (Altman et al. 1968; Cain & Routtenberg 1983; Meaney et al. 1985; Wilson et al. 1986); it is therefore possible that the hippocampus-accumbens circuit is involved in the behavioural deficits of nonhandled males (Feldon & Weiner 1988; in press a). Thus, nonhandling in infancy may provide an animal neurodevelopmental model of those schizophrenic-like cognitive abnormalities that are modelled in normal animals by amphetamine administration or manipulation of the hippocampal system.

It is suggested by **Pilowsky & Murray** that the faulty behavior to which the structural abnormalities of the brain give rise in schizophrenia (in their view, however,

in only the "chronic" form of this illness) consists of the negative symptoms. This view is supported by the association (see above) between negative symptoms and such measurements of structural abnormality as ventricular enlargement and decreased brain weight (Murray et al. 1988; Cannon et al. in press). We would be happier to accept this view if it had support from specific behavioural tests applicable to negative symptoms and to the relevant structural limbic pathology in the same way that we believe LI and KE are applicable to positive symptoms and the relevant functional changes in the limbic system and basal ganglia. Indeed, construction of such behavioural tests is now, in our view, a pressing need.

It is possible that we have actually stumbled on one such test. As outlined in the target article, the PREE has many of the same credentials as LI and KE as a test of the cognitive dysfunction underlying schizophrenic positive symptoms: It is abolished by amphetamine, damage to the septohippocampal system (SHS), section of the subiculo-accumbens pathway, and electrolytic lesions of n. accumbens (for references see target article; and unpublished data from Rawlins's laboratory). Note, however, that other work on the PREE (behavioural, pharmacological, and involving interventions in the brain) indicates that more than one process can produce this phenomenon (Gray 1982a); in particular, the effects on the PREE of amphetamine and damage to the SHS, respectively, depend on different parameters (**Weiner;** see, e.g., Feldon & Weiner 1989; Feldon et al. 1989; Rawlins et al. 1980). It is likely, in human as well as in animal subjects, that there will be more than one process affecting the PREE; it is highly unlikely, however, that the relevant parameters will take identical values in the two species. Thus, in taking this paradigm to the human level, it is difficult to predict in advance which type of PREE one is likely to generate with any particular experimental design. Recently, N. S. Gray (unpublished data) has completed a relevant set of experiments using a design modified from one developed by Vogel-Sprott (1967). She was able to replicate this worker's demonstration of a PREE (i.e., greater resistance to extinction after partial monetary reinforcement, PRF, for entering a four-digit number into a computer keyboard, compared to continuous reinforcement, CRF, of this response). The question then arose, was this PREE sensitive to amphetamine? In the same subjects who showed loss of LI in response to 5 mg amphetamine, the PREE was unchanged. It could now be predicted that if the PREE using this paradigm was altered in schizophrenia, this should be the case in both acute and chronic patients. The results N. S. Gray obtained (Figure 2) were not conclusive, but showed a marked reduction of the PREE in both patient groups, which did not differ from each other. Furthermore, the attenuation of the PREE was entirely the result of significantly increased resistance to extinction in the CRF condition. This is a pattern of change observed after some types of damage to the SHS (e.g., Brunner et al. 1974), but not after amphetamine administration (Weiner et al. 1985), which eliminates the PREE entirely because of reduced resistance to extinction in PRF subjects. (We note in passing that N. S. Gray's result does not agree with **Salzinger**'s statement that schizophrenics extinguish more rapidly than normal subjects; and we wonder how immediacy theory would predict the

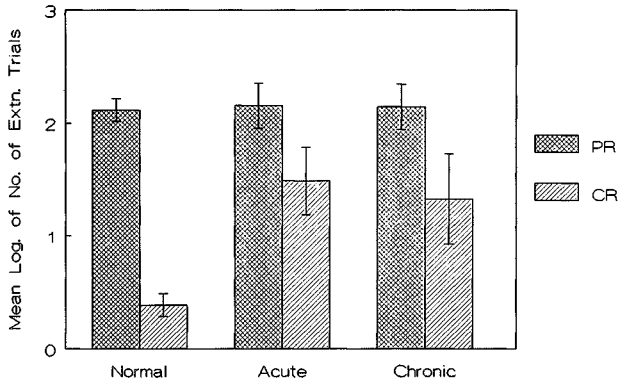

Figure 2. Mean log. of number of extinction trials as a function of reinforcement schedule and acute vs. chronic schizophrenia. Error bars indicate the standard error of the mean. PR = partial reinforcement. CR = continuous reinforcement.

pattern of results shown in Figure 2.) Here, then, we may have a test of the behavioural effects of the structural abnormalities in the SHS postulated by our model. If so, the PREE in this paradigm can now be used to test whether these abnormalities are related to negative symptoms.

Recently, it has been shown in rats that the critical feature that determines the PREE's sensitivity to amphetamine may be whether or not it is context dependent (Feldon & Weiner, in press b). Thus, when the experimental parameters of the PRF are set so as to encourage contextual mediation between the experience of nonreinforcement and subsequent reinforcement, amphetamine-treated animals fail to develop the resistance to extinction seen in normal controls. Extrapolating from these results to the human level, we would predict that the type of PREE that would be disrupted in acute but not chronic schizophrenics (or by amphetamine in normal subjects) is one that depends on learning about contexts (see further discussion of the importance of context, below).

The argument so far, then, treats structural abnormalities in the limbic system as a vulnerability factor, perhaps related to negative symptoms. This leads to the question of what triggers DA overactivity, giving rise to the episodic positive symptoms characteristic of acute schizophrenia. Some possible answers to this question were suggested in the previous section, but we accept that this remains a weak link in the argument, both theoretically and empirically.

A second mechanism that might underlie negative symptoms was suggested by **Sandyk & Kay,** in their illuminating parallel between both the profile of biochemical and pharmacological disturbance and the clinical picture in negative-symptom schizophrenia, on the one hand, and Parkinson's disease, on the other. These authors also question our claim that the neuropathology of schizophrenia fails to show morphological abnormalities in regions rich in dopaminergic cell bodies or terminals. Against this claim they cite a number of reports of pathology in the basal ganglia (though, we note, particularly in the globus pallidus, which is not a major target of dopaminergic innervation), as well as a study by Woodard (1962) in which Lewy bodies, like those seen in Parkinson's disease and with a similar regional distribution, were found in the schizophrenic brain. Clearly,

more data are needed to buttress these parallels; but the case Sandyk & Kay make is strong enough, in our view, to warrant serious investigation of the possibility that negative symptoms reflect underactive dopaminergic transmission, just as positive symptoms may reflect overactive dopaminergic transmission. Such underactivity might either occur at times other than when DA overactivity occurs, giving rise to the fluctuating course of schizophrenic symptoms; or it may occur at the same time but in different DA systems (e.g., as in Weinberger's 1987 model, underactivity in the mesocortical DA system coexisting with overactivity in the mesolimbic system).

A third possibility was suggested by **Sarter,** as a consequence of the loss of limbic excitatory inputs to n. accumbens and the resulting dopaminergic hyperactivity within accumbens postulated in our model. This should lead (Sarter proposes) to a reduction in the GABAergic output from accumbens to the cholinergic neurons of the ventral pallidum. The reduced inhibition of the latter neurons should in turn give rise to hyperactivity in the cholinergic innervation of the neocortex. Sarter then cites evidence (Tandon & Greden 1989) implicating cholinergic hyperactivity in the negative symptoms of schizophrenia.

These three neural hypotheses concerning the relationship between positive and negative symptoms – one based on limbic structural pathology, one on functional DA underactivity, and one on cholinergic hyperactivity – are clearly different in kind from the psychological hypothesis proposed in the target article, according to which negative symptoms represent adaptive behavioural strategies designed to cope with the distressing effects of positive symptoms. We accept the criticism that this hypothesis cannot account for all negative symptoms, since it wrongly predicts that negative symptoms are invariably preceded by positive ones (**Manschrek & Maher**). The possibility still remains, however, that the coping hypothesis is correctly applicable to some negative symptoms in some patients. This is an area to which careful longitudinal studies of individual patients might make a valuable contribution. Such studies would be greatly helped by the application of appropriate behavioural tests, such as the PREE (see above) or tests known to be sensitive to cognitive deficits in Parkinson's disease or to the action of cholinergic drugs, as well as detailed description of the temporal course of different symptoms.

9. State or trait?

Another useful approach, discussed by **Claridge & Beech, Elkins & Cromwell, Raine & Cannon,** and **Venables,** is the study of either relatives of schizophrenics or normal individuals with elevated scores on personality traits thought to be related to psychosis, for example, the Eysencks's (1975a) P scale or Claridge & Broks's (1984) Schizotypy (STA) scale. If a particular form of behaviour, observed in schizophrenia, is found in such individuals who are not (or at least not yet) themselves schizophrenic, it is plausibly more closely related to a structural (trait) than to a functional (state) characteristic. We have indeed applied this approach by attempting to relate the size of both LI and KE in normal subjects to relevant personality traits. We have found little consistency, however, in the results we have obtained (in great contrast to the replicability of the results we have obtained with schizophrenics). In a first study (Baruch et al. 1988b) we found reduced LI in high scorers on the Eysenck P scale (as predicted), but not on the STA or Launay & Slade's (1981) measure of the tendency to experience hallucinations. Even the significant relationship between LI and the P scale was not replicated by N. S. Gray (unpublished data); though we note from **Lubow**'s commentary that confirmatory data appear to have been gathered by Zaks in his laboratory. Furthermore, Jones et al. (1990) found no relationship between the size of KE and any of the above scales. Thus, overall, these results concur with the other data, summarised above, in suggesting that impaired LI and KE are the result of a state factor, viz, elevated DA transmission. This inference requires further testing, however, using high-risk relatives of schizophrenics. In this connection, we note with interest Raine & Cannon's citation, as an instance of impaired LI, of Mednick's & Schulsinger's (1968) observation of larger skin conductance responses to a preexposed CS in the children of schizophrenics.

10. Latent inhibition and habituation

Impaired LI, then, most probably reflects a state change characteristic of the hyperdopaminergic state present in acute schizophrenia. But what does this mean in psychological terms? This was an issue raised, in different ways, by a number of commentators.

Claridge & Beech and **Dawson & Hazlett** equate loss of LI with impaired habituation of the orienting response. These two phenomena can clearly be dissociated, at least under some circumstances (e.g., Hall & Channel 1985a), however, so any inferences based on this premise must be considered doubtful from the start. Moreover, Claridge & Beech's assertion that LI 'merely represents a form of habituation' itself merely represents one theoretical view of the phenomenon (that outlined by Wagner 1978), and, in any case, leaves *which* form dangerously unspecified. Wagner's (1978) view was that long-term habituation and LI were identical, but that short-term habituation has a different basis. Thus, studies of habituation in schizophrenics would have to be (demonstrably) studies of *long-term* habituation if they are to have any relevance to our model; and even then, their relevance would depend upon accepting Wagner's view of the phenomenon, rather than, for example, Mackintosh's (1975) view. These difficulties in interpretation may underlie the disparate views of habituation in schizophrenic patients presented by **Claridge & Beech** and by **Schmajuk & DiCarlo** (in their Table 1), on the one hand, and by **Dawson & Hazlett** on the other. Although we accept the judgment of Dawson & Hazlett that the most frequent abnormality reported in schizophrenics is the *lack* of an orienting response, Zahn (1988, p. 205) has reviewed work suggesting that acute unmedicated schizophrenics (to which the *alleged* prediction from our model would best apply) frequently exhibit "a pattern of slow rates of adaptation to novel stimuli." Mirkin (1985) has also reported a pattern of hyper-responding in acute schizophrenics, arguing that the crucial factor was the presence of positive symptomatology. A resolution of the empirical

issue would require the use of better-specified experimental procedures in testing patients. Moreover, the difference sometimes reported between LI and habituation is itself a theoretically important one: LI is context specific (i.e., it is disrupted by context shift), whereas habituation is not (Lubow 1989; McLaren et al. 1989, and references therein), a point noted by **Frith, Gewirtz,** and especially **Lubow.**

11. Selective attention or learning about context?

The dependence of LI on context may have particular significance for its relation to schizophrenia. For, as pointed out in different ways by many commentators (**Dawson & Hazlett, Frith, Harrow & Silverstein, Lubow, Oades, Patterson, Salzinger,** and **Venables**), a key cognitive deficit in schizophrenia may consist in the failure to relate specific associations to the context (retrieved, as Harrow & Silverstein emphasise, from long-term memory, LTM) in which they occur. In the case of LI, the association in question is one of stimulus-no consequence (Lubow); a failure to link this association to its context should have the same consequences as a context shift, i.e., abolition of LI, and this may indeed be the most appropriate account of the loss of LI in acute schizophrenics. The commentators listed above point to a number of schizophrenic symptoms that can plausibly be derived from the postulated lack of control by context; it is important to note that they include symptoms involving language, of which Frith provides an illuminating account. Assuming, therefore, that habituation of orienting responses is not slowed in acute schizophrenia (although this is clearly an issue deserving more study, preferably along with simultaneous measurement of LI), the dependence of LI, but not of habituation, on context could provide a theoretically satisfying account of the different relation of these two phenomena to acute schizophrenia. Dawson & Hazlett point to the fact that LI and KE both involve a *change* in the meaning of past regularities; we treat this as another variant of the general concept of "context" on the grounds that, if one is less tied to context (as the above argument supposes the acute schizophrenic to be), one can more readily detect a changed significance of a stimulus when the context does not change (manifest as loss of LI and KE).

More generally, we agree with **Frith** that "studying tasks that involve the processes by which context determines relevance will enable us to understand the symptoms of schizophrenia"; we also find that his analysis of "relevance" in terms of contextual dependence (in place of, or perhaps alongside, the analysis in the target article in terms of relationships to motor programming) has much to recommend it. Studies of the role of contextual dependence in schizophrenic cognitive performance may, in addition, help to determine the scope of our view that schizophrenia reflects a "weakening of the influence of stored memories of past regularities of previous input on current perception" (Hemsley 1987a) or general "over-attention" (target article). We accept the criticism that, put this baldly, these theories predict deficits in too many tasks, including even simple conditioning and learning (**Frith, Gewirtz, Spohn**). A testable hypothesis worth taking seriously is that acute schizophrenics will be impaired on tasks that are sensitive to context shift, but not on tasks insensitive to such shifts.

Two of the tasks recommended by **Frith** for studying the role of context are conditional discrimination (e.g., "if A do X, if B do Y") and reversal learning, in which the rules governing responding are changed after initial learning (e.g., "if A do X, if B do Y" changing to "if B do X, if A do Y"). Performance in both these tasks is impaired by hippocampal lesions in animals (**Oades;** and, for review, Gray 1982a); we have also recently demonstrated impaired conditional discrimination learning in human subjects with unilateral temporal lobectomy (Daum et al., in press). Data on conditional discrimination in schizophrenia would, we agree, be of considerable value, as would such data on reversal learning. In the latter case, however, prediction is unclear. Frith cites the work of Ridley et al. (1981) as showing that amphetamine disrupts reversal learning in marmosets; but **Weiner** notes that, in rats, her group has reported that amphetamine facilitates reversal learning (Weiner et al. 1986a; 1986b; 1987a; Weiner & Feldon 1986), thus having different effects from those of hippocampal lesions (Gray 1982a). As indicated by **Dawson & Hazlett,** just such a facilitation of reversal learning can be predicted for acute schizophrenics on the basis of their (contextual) interpretation of Hemsley's (1987a) model.

As pointed out by Weiner and Feldon (1986), one reason for the discrepancy between Ridley's (1981) results and their own could stem from the fact that in the former study the monkeys were tested following *repeated* reversal training. Under these conditions, monkeys acquire a learning set for reversal, and it is probably this reversal set that is disrupted by amphetamine. It can be argued that the animals' performance in such a design depends critically on their ability to use local context (for instance, a series of nonreinforced outcomes resulting from repeated selection of the current stimulus) as a signal to switch responses. A deficit in contextual learning would therefore lead to poorer performance in repeated reversals (or in repeated reacquisition and re-extinction tasks). Thus, a consistent action of amphetamine could both facilitate single reversal *and* retard repeated reversals, by reducing the extent to which context controls behaviour. Furthermore, the amphetamine-induced facilitation of single reversal is consistent with the effects of this drug on LI and the PREE. More generally, amphetamine-treated animals fail to apply previous experience under changed reinforcement contingencies and appear to be under an exaggerated control of the prevailing situational demands (Weiner & Feldon 1986).

With regard to the actual performance of schizophrenics on this task, **Schmajuk & DiCarlo** state in their Table 1 that there is a deficit. We are aware of one study (Nolan 1968) that did indeed demonstrate such a deficit. S. Georgiades (personal communication) found no such deficit in either acute or chronic schizophrenics, however. His data instead indicate something more complex: a loss of the overlearning reversal effect (ORE, i.e., the facilitation of reversal normally produced by overtraining on the initial discrimination) in both groups of patients, who, relative to normal controls, displayed (nonsignificantly) faster reversal in the nonovertrained condition coupled with slower reversal in the overtrained condition. Given Sutherland & Mackintosh's (1971) well-

known analysis of the ORE as reflecting increased attention to relevant stimulus dimensions in consequence of overtraining, this is a theoretically interesting result that is likely to repay further investigation. It is an important result, also, in that it closely resembles the effects of amphetamine in the rat: Weiner et al. (1986a) showed that this drug eliminated the ORE while facilitating reversal particularly in nonovertrained animals. Note, however, that our general logic would lead us to predict from Weiner et al.'s (1986a) findings that only acute schizophrenics should fail to display an ORE (as we did for LI), yet Georgiades's results show loss of the ORE in both acute and chronic groups. Knowledge of the effects of hippocampal lesions on the ORE might throw light on the cause of this discrepancy, but we are unaware of any relevant data. Also valuable would be data on the effects of amphetamine on the ORE, in Georgiades's paradigm, in human subjects (cf. the discussion of N. S. Gray's data on the PREE displayed in Figure 2).

We have recently conducted one further study devoted to these issues. As well as being relevant to the role of context in determining schizophrenic performance, this study addressed a further issue raised by **Spohn** and **Stevens & Gold,** namely, whether it is correct to describe the cognitive deficits of acute schizophrenia as "attentional"; and, if so, whether the deficit is one of over-attention, as stated in the target article, or under-attention. This point was also addressed, though in different terms, by **Schmajuk & DiCarlo,** who would prefer to see the relevant attentional constructs expressed more precisely, within formal learning-theoretic models.

More generally, **Frith** and **Hestenes** feel that our model would gain greatly if its verbal descriptions were superseded by a formulation in computational, especially neural-network, terms. We agree that this indeed is the way to go, and note that the two types of model (learning theory and neural network) have much in common (see McLaren et al. 1989, for a specific example of this overlap as applied to LI). However, the time to do this will be when specific predictions that can be tested at the appropriate level (including, critically, with schizophrenic patients) can be derived from one but not other such models. (The same point can be made with reference to models expressed in terms of "tightly defined, time delimited, information processing stages," as advocated by **Patterson.**) We doubt that that time has yet come, though it has been brought nearer by two of the current commentaries (**Schmajuk & DiCarlo** and **Gewirtz**) that picked out the Pearce-Hall (1980) model for its congruence with some of the ideas we expressed in verbal terms.

At a cruder level than this, our own recent experiment (Jones, Hemsley & Gray, unpublished data) aimed to contrast a general selective attentional hypothesis with one that focuses on context-dependent associations (in most cases the two types of hypothesis tend to make the same predictions). The experiment used a choice reaction-time paradigm derived from Eriksen & Eriksen (1974) and developed by Miller (1987). The subject had to make one of two responses to two visually presented letters (e.g., *A*, *B*). These targets were regularly accompanied by two flanking letters (e.g., *X*, *Y*), making displays of the form, *XAX* or *YBY*. Occasionally, the flanking letters were interchanged (*YAY* or *XBX*), but the correct response was still cued by the target (*A* or *B*). Normal subjects show a reliable slowing of reaction time on such context-shift (transposing of *X* and *Y*) trials. Now, if acute schizophrenics have a broader span of attention, they should be more aware of the flanking letters and so should show a greater-than-normal slowing of reaction time on context-shift trials. But if they do not readily make associations between focal stimuli and context, they should be less affected than normal subjects by context shift. The latter is the result found by Jones, Hemsley & Gray in acute, but not chronic, schizophrenics. Since this is the same contrast as that found for LI, it suggests that the account of loss of LI in terms of impaired contextual learning, given above, may be along the right lines. Thus the criticisms of our use of the concept of "over-attention", made by a number of commentators (see above) are not without foundation. Note, however, that a shift in emphasis from an attentional construct to one emphasising context-dependent access to stored regularities remains consistent with the general neuroanatomical basis of our model. Indeed, there is much evidence that the hippocampal formation plays an important role in learning about context in animals (Gray 1982a, for review; Winocur et al. 1987), a role that also appears to be played by temporal lobe structures in man (Daum et al., in press).

Likewise congruent with these arguments, as pointed out by **Venables** (and see **Dougherty et al.** and **Oades**), are data on event related scalp potentials. In particular, P300 appears to be related to the extent to which an important and relatively novel stimulus "engages the subject's attentional resources and makes it necessary for the subject to update his model of the context in which the stimulus occurs" (Anscombe 1987, p. 244); furthermore, P300 is reduced in schizophrenia, and this reduction may reflect hippocampal pathology (Halgren et al. 1980). On the other hand, as noted in an earlier section, the reduced P300 amplitude appears to be associated with negative rather than positive symptoms (Venables).

With the above clarifications, then, we believe that Hemsley's (1987) view (which wins the approval of **Elkins & Cromwell**) of schizophrenic cognitive abnormalities in terms of a reduced influence of past regularities on current perception can stand. As **Salzinger** observes, there are some similarities between this view and his "immediacy theory." Spohn (1984, p. 354) has indicated that there are problems in defining what, in a given situation, is the "immediate" stimulus, however, paralelling some of Salzinger's criticisms of the present model. This weakens the force of post hoc comparisons of the explanatory power of the two hypotheses; a clear experimental test of differential predictions derived in advance would, however, be of value.

12. Controlled versus automatic processing

It is not claimed that the "memories of past regularities" of Hemsley's (1987a) formulation are not stored, or that they are inaccessible. They may indeed be accessed by consciously controlled processing. Although **Oades** implies that we view controlled processing as defective in schizophrenia, this is not the case. Rather, the suggestion is that the rapid and automatic assessment of the significance, or

lack of significance, of aspects of sensory input (and their implications for action) is impaired, as a result of a weakening of the (context-dependent?) influence of stored past regularities. This psychological deficit reflects the impaired operation of the subiculo-accumbens projection (sect. 9 of target article). Such a failure of automatic processing could lead to the altered perceptual experiences noted by Matussek (1952; see also **Lubow**). In addition, it could place extra demands on the operations of a controlled processing system (**Nuechterlein & Green**; cf. Nuechterlein & Dawson 1984, p. 193).

We are impressed by the parallels, pointed out by **Gewirtz**, between Pearce & Hall's (1980) model, our own, and the general notion of the transition from automatic to controlled processing (Schneider & Schiffrin 1977). As Gewirtz points out, however, the scope of the Pearce & Hall model is much wider than our own data would allow in accounting for the consequences of manipulation of the subiculo-accumbens projection or of ventral striatal dopamine systems. Therefore we do not feel that we can simply treat the basis for our reductions of LI as identical to the mechanism whereby CS associability is reduced in the Pearce & Hall model. That would presumably entail the prediction that acquisition over a number of trials of simple CS-US pairings would take place at a different rate in normals (for whom associability should steadily decline during acquisition) and in animals given amphetamine (for whom associability, and hence the rate of increase in associative strength, should be constant until maximum associative strength is attained). We would not wish to make such a prediction. We accordingly regard the similarities as intriguing, but no more than that for now.

13. The plausibility of the model in relation to symptom formation

So far, we have considered the psychology of the model in relation to criticisms of a primarily theoretical nature. There were also those who saw its relation to schizophrenic symptoms as unconvincing (**Salzinger, Stevens & Gold**). Because the target article suggests that "the least satisfactory application of Hemsley's hypothesis is to hallucinations," at least one of the authors is pleased with (though reluctant to accept) **Patterson**'s view that these are "epiphenomena." In reply to Stevens & Gold, we would see the reduction in the organisation of current sensory input (because of a weakened influence of past regularities) as facilitating the intrusion into awareness of (i) elements that are normally processed outside consciousness (because redundant), and (ii) material from LTM. (To this, **Harrow & Silverstein** add a valuable discussion of how a weakening of long-term memory for contextual constraints might facilitate the schizophrenic's acceptance as "real" of experiences that would be rejected by normal individuals.) Given the constructive nature of normal recall, the intrusions from LTM would not necessarily be identical to previously presented material, as supposed by Stevens & Gold.

Hoffman poses a challenge that we shall not accept: to account for the particular (and not very typical) symptoms of a particular patient. **Swerdlow** poses another: to predict therapeutic response. We know our limitations!

14. Hemispheric lateralisation

We were severely taken to task for having neglected the large and important literature on lateralisation of schizophrenic abnormalities (**Claridge & Beech, Elkins & Cromwell, Raine & Cannon, Spohn**); as Elkins & Cromwell put it, "it seems strange that the extensive body of laterality research is not even mentioned" in the target article. This omission did not betoken any lack of appreciation of the importance of the relevant literature. It stemmed, rather, from our perception of the function of a model like the one we were bent on constructing: to make new and specific integrations and predictions. The items we were putting together into our model included important elements from research with animals. These elements, as is typical for data relating to animals, were unrelated to hemispheric laterality (although **Goldberg**'s view of hemispheric specialisation in animals may be applicable to some of them). At the time, of writing the target article we therefore had nothing to add to the existing literature on this topic; nor did we feel that this literature substantially affected what we had to say.

If the commentaries had left us in any doubt that this was nonetheless too important a topic to leave shrouded in silence, our own data have forced us (like so many researchers before us) into the laterality field, for two of our key experiments have turned out to involve major laterality effects.

First, N. S. Gray (unpublished data) has demonstrated that, in normal subjects, the Baruch et al. (1988a; 1988b) paradigm produces LI if the conditioned stimulus (CS) is presented to the left ear, but not if it is presented to the right ear; bilateral presentation of the CS also produces LI. The reasons for this laterality effect are at present unknown. Given the complexity of the ipsi- and contralateral projections of the auditory system, we can not yet even interpret the ear effect as a hemisphere effect. Nor do we know whether LI is lateralised in general, or whether the effect is because of some inessential feature of our paradigm (e.g., the use of verbal masking material). We do know, however, that the effect of amphetamine on LI is also lateralised. With left-ear presentation, the data exactly fit prediction: LI was abolished by a low (5 mg) dose but left intact with a high (10 mg) dose. With right-ear presentation, however, a quite unexpected pattern was seen: Both the 5 and the 10 mg dose appeared to give rise to LI (which was absent in the placebo condition; N. S. Gray, unpublished data). This pattern *may* reflect the left-biased asymmetry in the hemispheric distribution of DA referred to by **Goldberg.** Given these results, it will be necessary to repeat our previous observations with schizophrenics (Baruch et al. 1988a) for each ear separately. To speed these experiments up, we have developed a within-subject LI paradigm (N. S. Gray & M. Peoples, unpublished data), which fortunately shows the same ear effects as the between-subject paradigm.

Second, in the experiment by Jones, Hemsley & Gray described earlier (section on Selective attention or learning about context?), using Miller's (1987) choice reaction-time paradigm, we found different patterns of results depending on the hand of response. Only with right-hand responses did we observe the effects described above, which we interpreted as indicating that acute schizophrenics fail to integrate context with a target stimulus-

response association. Fortunately, hand of response offers a more direct hemispheric analysis than does ear of stimulation; thus, we may take this result to be congruent with the body of research indicating principally left-hemisphere dysfunction in schizophrenia (**Goldberg, Raine & Cannon**). Given recent evidence that the lateralisation of structural abnormalities in the schizophrenic brain is particularly marked in the temporal lobe, including the hippocampal formation and amygdala (Crow, in press; Deakin et al. 1989), these results are in good agreement with the hypothesis that abnormalities of learning about context reflect (left-sided) hippocampal pathology (see the earlier discussion above).

It is rapidly becoming possible, therefore, to integrate the model presented in the target article with the important body of literature on lateralised pathology and dysfunction in schizophrenia; and it seems likely that asymmetries in both DA distribution (**Goldberg**) and hippocampal pathology (Goldberg, **Raine & Cannon**) will figure in this integration.

15. Input dysfunction

The basic criticism made by **Elkins & Cromwell** is that we have ignored the "huge body of data and theory that focuses on stimulus input (e.g., Venables 1964) as the primary dysfunction in schizophrenia." This view is lent weight by abnormalities of schizophrenic information processing detectable at times after stimulus onset as brief as 6 msec (**Patterson,** citing Bick & Kinsbourne's 1987 report on brainstem auditory evoked responses) or 10–80 msec (**Oades,** citing research on tachistocopically presented flashes reviewed by Straube & Oades 1991). As Elkins & Cromwell recognise, however, given the way we have constructed our model, this is an area to which we are unlikely to have much to contribute.

16. Motor programming

The emphasis given in our model to the motor programming functions of the basal ganglia, and consequently to disturbances in such programming as playing a central role in schizophrenic abnormalities, met with a mixed reception.

Swerdlow turns the tables on a previous commentary of our own (Gray & Baruch 1987) on the Swerdlow & Koob (1987) *BBS* target article. Our complaint had been that the Swerdlow & Koob model left out the cognitive and emotional disturbances by which schizophrenia is above all defined; Swerdlow believes that the same is true of our emphasis on motor programming. (He does, however, accept that our model has helped put the "psych" back into the neuropsychology of schizophrenia. **Claridge & Beech,** in contrast, accuse us of leaving out the 'psyche.' Perhaps it all turns on the significance of that final 'e'.) **Pilowsky & Murray** and **Stevens & Gold** also have difficulty in accepting our treatment of "cognitive abnormalities in acute schizophrenia as a special kind of disorder in motor programming and monitoring." We would ask these authors: What other kind of process can the sequencing of words in sentences (including the subvocal words that make up so much of thought) be besides one of motor programming? That this is indeed a reasonable view of linguistic cognitive processing is endorsed by **Oke & Adams,** who provide a valuable discussion of the neurological basis of this processing. Finally, **Crider** is the commentator who goes furthest in his support for a motor-programming approach to schizophrenia, pointing out that available data support the implication of our model that there should be a "relationship between motor disturbance and cognitive dysfunction" in this condition (Manschrek 1986; Yarden & Discipio 1971), and suggesting that "motor signs may be as valid as cognitive symptoms in defining the psychotic state in schizophrenia." We agree that this hypothesis is well worth attention, perhaps by studying covariation between schizophrenic cognitive and motor abnormalities, respectively, in the manner briefly reviewed in **Early & Haller**'s commentary (cf. Bracha 1987; Posner et al. 1988).

17. The model for motor programming

The structural and functional details of our model of motor programming in the basal ganglia, in interaction with limbic inputs from the septohippocampal system and amygdala, similarly met with a mixed reception. General approval was forthcoming from **Cools & Ellenbrook, Crider, Swerdlow** (on whose work with Koob much of our model was based), **Weiner** and **Williams.** But many searching criticisms, queries, or alternative possibilities were also raised.

Carlsson & Carlsson believe that loop II of Figures 5 and 6 of the target article provides negative feedback, whereas we followed Swerdlow & Koob (1987) in treating it as a positive feedback loop. We agree that these loops need further investigation to clarify their more detailed circuitry. Carlsson & Carlsson also query the attribution of a switching function (between steps in a motor program or between motor programs themselves) to the dopaminergic signal that terminates operation of loop III; this assumption is strongly endorsed by **Cools & Ellenbroek,** however; work from their laboratory has provided much of the relevant supporting evidence. Carlsson & Carlsson offer evidence that the switching function is instead mediated by a glutamatergic mechanism; this evidence is not incompatible with our model, however, because this treats switching as the result of the interaction between two presumed glutamatergic inputs to n. accumbens (from the subiculum and amygdala) and the dopaminergic input from A 10. Although Cools & Ellenbroek accept our general approach to the neural basis of the switching function, they cite evidence that the striatal and accumbens systems do not function in tandem (as supposed in our model; see Assumptions 2 and 7 in sections 9 of the target article), but more like "a seesaw." **Weiner** accepts the notion that the striatal and accumbens systems function jointly, but suggests that the operation of the three loops of which each is made up occurs in a staggered manner, coordinated by way of the projection from n. accumbens to substantia nigra (Figure 10 of target article). We are impressed by her specific proposals for the integrated running of the two systems and would like to incorporate them into our model. **Pisa & Cleghorn** query the suggestion that "dopaminergic neurons discharge at the end of ongoing motor programs," and state that single

unit studies of dopaminergic neurons do not support this suggestion. But *our* suggestion is that these neurons discharge at the end of each *step* in a motor program; and furthermore, given Weiner's suggested modification, above, in a staggered manner between A 10 and nigral neurons.

The theme of timing of activity in the interacting basal ganglia and septohippocampal systems is imaginatively advanced by **Williams,** who takes up the suggestion in the target article that such timing is coordinated by the hippocampal theta rhythm. As he points out, the timing of the subicular input to accumbens (of which more below) is critical: "Any signal at the wrong time is the wrong signal." From this, it follows that "schizophrenic symptoms may arise from disruption of the SHS EEG theta rhythm." Williams shows how (given the control of theta by the cholinergic septohippocampal projection) this argument can integrate evidence that schizophrenia is linked with abnormal septal spike activity (Heath & Walker 1985) and medial septal structural abnormalities (Lewis & Mezey 1985), as well as the psychotomimetic effects of theta-disrupting anticholinergic drugs (see also **Frith** on the effects of lesions to the cholinergic septohippocampal projection). (We draw the attention of **Stevens & Gold** to **Williams**'s commentary by way of an answer to their query about the relation of the septohippocampal cholinergic projection to our model.) Williams also takes up the distinction made by Gray (1982a) between high-frequency "checking" mode theta and low-frequency "control" mode theta, and makes the interesting suggestion that the former relates to the timing of steps in a motor program (and to automatic processing, in the sense of Schneider & Shiffrin 1977) and the latter, to the transition between different motor programs (and to controlled processing). Both the integration of existing data and the suggestions for future research contained in this commentary are of great value. It may also be fruitful to link these suggestions with the intriguing observation (**Venables**) that the slow reaction time of schizophrenics is not a continuous function but exhibits "time quanta of 100 msec."

Cools & Ellenbroek and **Pisa & Cleghorn** suggest that some of the deficits seen in schizophrenia may be of striatal rather than accumbens origin; this view fits well with **Crider**'s that motor disturbances, including in particular stereotypies (well known to be associated with striatal dysfunction in animals), are characteristics of schizophrenia; a similar point is made by Pisa & Cleghorn. (Incidentally, Crider's views on this score seem to be particularly appropriate to **Hoffman**'s patient.) Motor stereotypies are also discussed by **Dougherty et al.**, who point to the possible role played in their development (and that of paranoid symptoms) by abnormal catecholaminergic reinforcement mechanisms.

Cools & Ellenbroek also question our treatment of the role of the basal ganglia in responding to novelty (see Assumption 9 of section 9, and Figures 8 and 9). They cite evidence that the noradrenergic input to n. accumbens is triggered by environmental challenge, giving rise to an inhibition of the subiculo-accumbens afferents; they also point to the relevance, in this context, of reports of elevated postmortem noradrenaline content in the accumbens of schizophrenic brains (a change that, according to **Stevens & Gold,** might be the result of heterotypic sprouting of noradrenergic fibres in response to a deficient subicular projection to n. accumbens). As Cools & Ellenbroek point out, although different in important matters of detail, their approach is consistent with our overall model; and the differences of detail are readily open to experimental study.

Carlsson & Carlsson, in contrast, attribute selective attention to novel stimuli to the thalamic input to cortex under dopaminergic control in such a manner that "increased dopaminergic activity would allow more information to reach the cortex." This suggestion fits well with **Oke & Adams** findings of "unusual" levels of DA in schizophrenic thalamic. In the absence of further data, however, it is difficult to integrate this approach with the key experimental observations on LI and KE, in both animals and patients, which underlie our model. This model clearly does allow a role for thalamic nuclei (see Figures 5 and 6 in target article). The thalamus is also emphasised in Oke & Adams's penetrating discussion of the role of this region in the programming of language, and therefore of the abnormalities of language characteristic of schizophrenia (see also **Patterson** on this point). They point out that projections from n. accumbens to the appropriate thalamic regions are unlikely to come directly or through other thalamic structures, leaving the prefrontal cortex as the most likely route for an interaction of this kind. This inference poses no problem in principle for our model, which indeed postulates just this route (see Figure 10 and Assumption 5 of section 9). It is clear from all the above, however, that thalamic function and its role within our overall model requires more elaborate consideration than it received in the target article.

18. The hippocampal formation

Several commentators (**Crusio, Early & Haller, Pisa & Cleghorn, Schmajuk & DiCarlo**) appear to assume that there is (or that we claim there is) a simple equation between schizophrenia and hippocampal (or subicular) lesions. This is certainly not our position; nor, as pointed out by Early & Haller and Pisa & Cleghorn, is it one that is supported by evidence from human beings with known hippocampal or temporal lobe lesions. From Gray's model of the functions of the SHS, which was incorporated with only slight changes into the target article, one can predict, rather, that hippocampectomy should give rise to reduced anxiety; much evidence with animals supports this view (Gray 1982a). Schmajuk & DiCarlo, in contrast, present a table purporting to show striking parallels between the behaviour of hippocampectomised animals and schizophrenic patients; we feel, however, that the generality of some of the results represented there is still too controversial. For example, there are conflicting reports about the effects of hippocampal lesions on habituation (Gray 1982a), and it seems likely that performance both on acquisition and extinction of classical conditioning in hippocampectomised animals may depend critically on the experimental conditions of training (e.g., data reviewed in Rawlins 1985). Similarly, in our view the behavioural evidence suggests that Crusio's strains of mice with small intrahippocampal mossy-fibre projections constitute better analogues of low anxiety (or poor

spatial ability: Crusio et al. 1987; Schwegler et al. 1990) than of any psychotic tendencies. (This is not to say, however, that we dispute Crusio's argument for a genetic role in schizophrenic, or that we claim this cannot be modelled in animals.) In our view, the neural basis of schizophrenia is to be found in the dynamic interplay between temporal lobe structures and the basal ganglia, not in a straightforward lesion. It is perhaps for this reason that psychotic symptoms characterise some individual with temporal lobe epilepsy (**Williams**) but not those with temporal lobe removal (**Early & Haller, Pisa & Cleghorn**). And it is for this reason that, in making our own clinical predictions, we relied on arguments jointly from the effects of damage to the SHS and those of manipulations of dopaminergic function. To this strategy, one can fruitfully add that of picking out those effects of SHS damage that are reversed by neuroleptics, as practised and advocated by **Oades.**

Oades asks why we focus on the subiculum at the expense of the entorhinal area and presubiculum, and on the subicular projection to n. accumbens at the expense of those to the septal area or hypothalamus. The answer again lies in our use of converging arguments to make predictions as tight as possible. The subicular projection to n. accumbens satisfies several requirements simultaneously in a way the others, as yet, do not. They may come to do so, however, in which case we would wish to apply parallel arguments to them. It is becoming apparent, for example, that the entorhinal area, like the subiculum, projects to n. accumbens (observations in Rawlins's laboratory); and we accept the findings described in Oades's commentary as indicating the possible importance of those regions of the septal area in receipt of both subicular and dopaminergic projections. **Oades** also believes that we have been too hasty in dismissing a role for noradrenergic systems in LI; we can only repeat that, in several experiments in Gray's (Tsaltas et al. 1984) and other laboratories (see Weiner 1990, p. 444, for review), we have been unable to see any effect on LI of near-total destruction of the dorsal ascending noradrenergic bundle (eliminating the noradrenergic projection to virtually all the regions implicated in LI).

19. The subiculo-accumbens projection

Whereas many commentators accepted the arguments indicating the importance of the subiculo-accumbens projection, there were many queries about the details of how this projection functions, and how it interacts with the dopaminergic projection to the accumbens. These questions concerned both the psychology and the physiology of this interaction; they are important, indeed central to our model.

On the psychological front, **Stevens & Gold** ask: What is the function of the input from subiculum to accumbens? The answer was given in some detail in sections 8 and 9. As **Pisa & Cleghorn** note, this function consists of sending to the accumbens information *either* that something unexpected has occurred ("mismatch") *or* that the preceding step in the motor program has had the expected sensory consequences ("match"). These commentators ask how the one subiculo-accumbens projection can mediate both these functions. Our answer (see sect. 8 and 9) is as follows: For "match," a topographically localised signal is sent from the subiculum by glutamatergic activation of a delimited set of presynaptic, inhibitory, dopaminergic terminals on accumbens Spiny I GABAergic output cells; this set is appropriate to the motor step that has just been completed; in consequence, this step is not repeated, allowing the amygdalar input to accumbens to select the next step for execution. For "mismatch," a generalised subicular input to accumbens interrupts all accumbens function relating to motor steps, allowing the activation of exploratory behaviour by the routes depicted in Figures 8 and 9. Thus, the key difference, insofar as the subicular output to accumbens is concerned, is that the "match" message is discrete, the "mismatch" message general. **Schmajuk & DiCarlo** ignore this double function attributed in our model to the subiculo-accumbens projection; they state roundly that it treats the hippocampal output to n. accumbens as "proportional to the mismatch between actual and predicted events," from which they deduce (though we cannot completely follow their argument) that the model cannot then account for KE. **Weiner,** although recognising the complexity of the model, prefers Gray's (1982a) earlier version, in which the SHS influenced motor programs (interrupting them) only in response to mismatch. [See also Näätänen: "The Role of Attention in Auditory Information Processing as Revealed by Event-Related Potentials and Other Brain Measures of Cognitive Function," *BBS* 13(2) 1990.]

We recognise that this confusion reflects difficulties with our model. **Weiner,** for example, correctly points out that by allowing the subiculo-accumbens projection to participate in the running of motor programs under conditions of match the target article ignores the evidence cited by Gray (1982a) as requiring the SHS to have no role in motor programming except when there is mismatch. Some of the evidence leading to this change of mind is discussed in section 9, in a passage whose uncertainties cause **Pisa & Cleghorn** to accuse us of "biting our own theoretical tails." But the uncertainties are real; and, in answer to the points raised (see above) by **Pisa & Cleghorn, Schmajuk & DiCarlo** and **Weiner,** we can plead only that more data are needed. We do not yet know, for example, whether section of the subiculo-accumbens pathway affects LI and KE (as, on our model as we have presented it, it should). Rawlins et al. (1989) reported that this operation clearly abolished the PREE; but data of equal clarity on LI have so far proved elusive, and the effort to obtain such data relating to KE has not yet begun (**Oades,** incidentally, effectively queries also the data cited in the target article concerning the effects of hippocampal lesions on KE.) The problems in pursuing this important line of research are largely technical. A form of surgery is needed that will selectively, consistently, and substantially destroy the subiculo-accumbens pathway. A way of selectively activating this pathway is also required. Work in Rawlins's laboratory is actively pursuing these goals.

Also questioned were the details of the postulated interactions between the subicular glutamatergic and A 10 dopaminergic inputs to accumbens. We agree that the details of these interactions remain unclear, and for that reason we indicated several different possibilities in the target article. Our general approach, namely, that there

is a functional equivalence between decreased subicular input and increased dopaminergic input to accumbens, met with approval from **Oades** and **Schmajuk & DiCarlo. Stevens & Gold** make valuable suggestions as to additional mechanisms, not considered by us, which might give rise (after damage to the subiculo-accumbens projection) to such a functional equivalence, namely, sprouting of dopaminergic fibres to take up vacated synapses, and a decrease in tonic inhibition of A 10 neurons by GABAergic feedback. On the other hand, they doubt the possibility, considered in the target article, that D2 binding sites might expand in response to damage to a glutamatergic input, because this would be more likely to increase glutamate binding itself. If observations made in the dorsal striatum can be regarded as relevant to considerations of ventral striatum, however, it is worth noting that the loss of cerebral cortical input to the caudate nucleus results in a consequent loss of dendritic spines there (Kemp & Powell 1971). Perhaps the loss of the retrohippocampal input to n. accumbens might result in an equivalent change, and thereby induce a radical reorganisation of the dopamine input. **Pisa & Cleghorn** point out that alteration in a system afferent only to n. accumbens would not be expected to lead to up-regulation of DA receptors in the dorsal striatum, as observed in the schizophrenic brain (Seeman et al. 1984). **Weiner** asks which mechanisms would determine whether the glutamatergic subicular input was mediated by local release of DA or not; both her commentary and that of **Carlsson & Carlsson** indicate possible factors (glutamate concentration, type of glutamate receptor, and anatomically distributed heterogeneity) affecting the interactions between glutamate and DA release. We can ourselves add only that this is deservedly an active area of research, and one can anticipate clarification of these issues in the near future. Fortunately, as pointed out by **Early & Haller,** our model is compatible with a number of different particular mechanisms that might mediate the general functional equivalence between reduced subicular inputs and increased dopaminergic inputs to n. accumbens that it postulates.

Weiner also provided a critical discussion of our analysis (sect. 10) of the way amphetamine affects behaviour in virtue of its actions in n. accumbens and the dorsal striatum. These issues are likewise best resolved by further detailed experiments; a particularly important role in such research is likely to be played by the application of in vivo neurochemical monitoring techniques to relevant brain regions in behaving animals (e.g., in a LI paradigm). Such experiments are currently in progress in Gray's laboratory (Joseph et al., in press). The detailed behavioural parameters that determine the action of amphetamine in the relevant paradigms are likely to play a vital role in distinguishing transmitter-behaviour relationships (observed in such in vivo monitoring experiments) that are causal from those that are adventitious. Thus we agree with Weiner on the importance of taking these parameters into account. We also agree that these parameters are often different from those that determine the effects of hippocampal lesions. But it is not correct, as she implies, that our model predicts that these parameters should be the same; rather, as pointed out earlier in this Response, we used similarity between the effects of amphetamine and hippocampal lesions, respectively, as a heuristic device to home in on phenomena for which we could make *converging* predictions.

20. The neocortex

Our model allowed roles in the pathology of schizophrenia for both temporal and frontal neocortex. However, apart from the postulate that the reduction of cholecystokinin (CCK) in schizophrenic temporal lobe (Roberts et al. 1983) reflects an impairment in the CCK-mediated input to the subiculo-accumbens projection (sect. 3, target article), we had nothing specifically new to add to previous accounts of these regions. This innovation drew little comment, except that **Pilowsky & Murray** questioned its significance in the light of recent evidence for low densities of CCK receptors in the human hippocampal region (Kohler & Chan-Palay 1988). Otherwise, we drew in particular on the hypotheses and work of Frith (1987; Frith & Done 1988a) and Weinberger (1987). The congruence between this work and our own model was accepted, and several commentators lent their weight to the view that abnormalities in both the frontal (**Frith, Goldberg**) and temporal (**Goldberg**) neocortex are likely to underlie aspects of schizophrenia.

Some of the relevant evidence with respect to the putative frontal lobe involvement is drawn from the Wisconsin Card Sorting Test (WCST) (**Dawson & Hazlett, Swerdlow**). Dawson & Hazlett comment, however, that deficits on this task (usually interpreted as showing an inability to change a conceptual set) are inconsistent with our findings that in the LI and KE tasks acute schizophrenics are *better* able to change behaviour (see the discussion of context effects earlier in this Response). We are unaware, however, of any study of the WCST using a control task matched for difficulty and discriminating power, as recommended by Chapman & Chapman (1978); thus, an interpretation in terms of generalised schizophrenic deficit has not been ruled out.

We were attracted by **Hoffman**'s suggestion that damage to the supplementary motor area of the frontal lobes (Goldberg 1985) might underlie the symptom of alien control; this suggestion fits particularly well with Frith's (1987; Frith & Done 1988a) model. We also find particular appeal in **Goldberg**'s treatment of some schizophrenic symptoms as a form of "associative agnosia" based on abnormal functioning of left temporal and frontal neocortex; this view is closely related to the notion of contextual dependence discussed earlier in this Response.

21. Psychotomimetic drugs

An important basis for our model is provided by amphetamine, whose effects in producing or exacerbating psychosis are well known. Several commentators cited other psychotomimetics with regard to the manner of their possible inclusion in the model. We have already noted in an earlier section **Williams**'s treatment of anticholinergics, whose psychotomimetic effects he attributes to disruption of control mode theta rhythm. This commentator similarly links the psychotomimetic effects of phencyclidine (PCP) to its capacity to disrupt checking

mode theta (Vanderwolf 1988). Because this compound blocks the ion channel associated with the NMDA class of glutamate receptors (particularly dense in the human SHS; Jansen et al. 1989a, 1989b), other commentators link its psychotomimetic effects to antagonism of transmission at the relevant glutamatergic synapses, including possibly those involved in conveying information from the limbic system to n. accumbens (**Hoffman, Jansen & Faull**). This hypothesis is compatible with **Williams**'s concerning hippocampal theta, and both are highly compatible with our model. Another possible mode of action of PCP and of other dissociative anaesthetics with psychotomimetic properties – ketamine, for example – is indicated by Jansen & Faull, viz, action at sigma receptors; these commentators remark that these receptors are densely distributed in the human n. accumbens and "other areas centrally involved in the model under discussion." We must point out, however, that, to our surprise, PCP does not disrupt LI (Feldon & Weiner, unpublished data) or the PREE (Clark et al., unpublished data) in the rat. Thus, loss of LI and the PREE may depend only on dopaminergic overactivity (in the nucleus accumbens), as suggested above.

Williams also points out that serotonin-depleting drugs disrupt checking mode theta. As he remarks, this may relate to our demonstration (Cassaday et al., in press) that drugs that reduce serotonergic transmission block LI, as does destruction specifically of the serotonergic innervation of the hippocampus. Here, then, may lie the basis of the psychotomimetic effect of LSD-25, about which **Claridge & Beech** ask (though we should note that we have so far been unable to produce a clear blockade of LI with this anti-serotonergic compound; Cassaday et al., in press). Thus, mechanisms certainly exist whereby nondopaminergic psychotomimetic drugs might modify activity in the brain systems implicated by our model. We do not yet know the degree of correspondence, however, between the effects of these different kinds of agents. Until we have further information on this point, we cannot assume that all psychotomimetics assert their effects through the same system.

22. Conclusion

The target article has indeed been the target of very wide-ranging comment and criticism. Most aspects of the model it contained have been covered, although we were surprised by the absence of a perspective from the thriving industry of molecular genetics. In general, we feel, the model has stood up well to the intense scrutiny it has received; we have certainly felt it necessary, however, to amend or extend it in a number of ways to meet our critics. We accept the need to limit our psychological model of the deficits of acute schizophrenia so that it does not predict too many deficits affecting *any* activity in which memory for stored regularities of past experience guides current perception and action. We accept also (guided in this change by some of our own recent data) that the tag "over-attention" may be misleading in its attempt to encapsulate the heart of our psychological model (though it does a good enough job in this respect for us not to abjure its use in the future). Both these problems may be overcome by a model that focuses more on context: That is, the acute schizophrenic cognitive abnormality would be particularly prominent under circumstances where the role of stored regularities in guiding current perception and action is context-dependent. Finally, we accept that we were wrong not to give some consideration to the way negative, as well as positive, symptoms are to be included in our model; we have so far, however, been able only to identify (with the help of the commentators) a number of alternative possibilities (not necessarily mutually exclusive) that would all be compatible with our basic model.

Our model therefore remains essentially as formulated in the target article (subject to the comments above, and with the addition of **Weiner**'s detailed suggestions concerning the joint timing of activity in the three loops of Figures 5 and 6). As endorsed by many commentators, the model is experimentally testable at many different levels. Comparisons between it and other similarly formulated theories – for example, Weinberger's (1987), Frith's (1987), and Swerdlow & Koob's (1987a) models – should lead to rapid progress in a field that is of central importance to psychiatry. The existence of such detailed neuropsychological theories, each capable of making specific and testable predictions, is sure evidence that schizophrenia has finally and fully entered the realm of neuroscientific research.

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